

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number  
**WO 2004/043457 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/397**,  
A61P 37/00

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,  
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,  
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(21) International Application Number:  
PCT/US2003/035058

**Declarations under Rule 4.17:**

(22) International Filing Date:  
4 November 2003 (04.11.2003)

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,  
CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, EG, ES,  
FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ,  
LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ,  
NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL,  
SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM,  
ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ,  
TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ,  
MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY,  
CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,  
NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/424,165 6 November 2002 (06.11.2002) US  
60/493,318 7 August 2003 (07.08.2003) US

— as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,  
BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, EG,  
ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ,  
LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI,  
NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM.

**Published:**

— with international search report  
— before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **CHOLESTEROL ABSORPTIONS INHIBITORS FOR THE TREATMENT OF AUTOIMMUNE DISORDERS**

(57) Abstract: The present invention provides methods for treating or preventing an autoimmune disorder and associated conditions by administering at least one sterol absorption inhibitor and compositions, therapeutic combinations and methods including: (a) at least one sterol absorption inhibitor; and (b) at least one autoimmune disorder treatment which can be useful for preventing or treating an autoimmune disorder and associated conditions.

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## CHOLESTEROL ABSORPTIONS INHIBITORS FOR THE TREATMENT OF AUTOIMMUNE DISORDERS

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority from U.S. Provisional Patent Application Serial No. 60/493,318, filed August 7, 2003 and U.S. Provisional Patent Application Serial No. 60/424,165, filed November 6, 2002.

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BACKGROUND OF THE INVENTIONField of the Invention

The present invention relates to methods and therapeutic combinations for treating and preventing an autoimmune disorder in a subject comprising the administration of sterol absorption inhibitor(s).

Description

The pathogenesis of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis and systemic lupus erythematosus is mediated by the aberrant activation, differentiation and trafficking of leukocytes in response to tissue self-antigens. There are two main types of leukocytes: phagocytes and lymphocytes. Lymphocytes, which include T-cells, B-cells and natural killer (NK) cells, play a large role in autoimmune reactions.

Plasma membranes of many cell types, including leukocytes contain domains enriched in cholesterol, plant sterols and sphingolipids called lipid rafts. The formation and organization of lipid rafts within cell membranes of leukocytes has been demonstrated to play a critical role in immune responses as diverse as T-cell activation, antigen presentation, adhesion molecule function and chemokine receptor signaling, as will now be discussed in further detail below.

Both cholesterol and sterols derived from plants have been shown to be essential to the structure and organization of lipid rafts, and to the subsequent downstream signaling events mediated by these rafts (see, Kabouridis, et al. (2002) Eur. J. Immunol. 30: 954-963; Bowen and London (2000) J. Biol. Chem. 275: 17221-

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17224; Burack, et al. (2002) J. Immunol. 169: 2837-2841; and Vu, et al. (2001) J. Biol. Chem. 276: 33540-33546).

It is known that lipid raft microdomains are important for T-cell receptor (TCR)-mediated activation of T-cells. Signaling proteins are associated with lipid rafts in T-cells and the TCR itself associates with lipid rafts (see Hreisi V. (2003) Immunol. Rev. 191: 1438-1464 and Janes et al. (2000) Immunology 12: 23-34). Furthermore, it has been shown that the integrity of lipid rafts containing the kinase Lck (a key signaling protein) is essential for the initiation of peripheral blood T-cell lymphoblasts (PBT) signal transduction through the TCR. It is also known that key signaling proteins such as Lck and LAT are physically sequestered into distinct lipid rafts in a resting T-cell. After activation, these signaling molecules coinhabit the same region within the plasma membrane, indicating that the sequestration of these proteins may function to regulate the initiation of T-cell signal transduction (Schade and Levine (2002) The Journal of Immunology 168: 2233-2239). Similarly, lipid rafts have been demonstrated to be essential for B lymphocyte activation (Cheng et al (2001) Semin Immunol 13:107-114), particularly in the context of Syk and CD45 tyrosine phosphatase colocalization (Gupta and DeFranco (2003) Mol Biol Cell 14:432-444). Given the role of lipid rafts in both T-cell and B-cell antigen receptor signaling, disrupting the formation and/or organization of these rafts will likely inhibit the aberrant activation of leukocytes in response to tissue self antigens that occurs in autoimmune disorders.

The importance of lipid rafts on antigen presenting cells (APCs) and their role in major histocompatibility (MHC) Class II - restricted antigen presentation is also known. T-cells use their antigen-specific receptors (TCRs) to recognize antigens (including self-antigens) bound to MHC molecules. MHC Class II molecules are known to be present in raft-like microdomains on APCs and perturbing APC raft integrity profoundly inhibits the ability of APCs to stimulate antigen-specific T-cells. Moreover, the localization of MHC Class II molecules into rafts on APCs allows APCs to efficiently present antigens (including self-antigens) to the TCR of antigen-specific T-cells, even at low concentrations of the antigen (Anderson, et al. (2000) Nature Immunology 1: 156:162). Furthermore, modification of a membrane cholesterol level has been previously shown to affect expression and clustering of

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Class I HLA molecules on the surface of JY human lymphoblasts (Bodnar, et al. (1996) *Immunol. Lett.* 54: 221-226). In view of these studies, it is likely that disrupting lipid rafts can inhibit the ability of APCs to stimulate autoreactive T-cells with autoantigens, and would be of benefit in treating/ preventing autoimmune disorders.

Adhesion molecules, such as integrins, are molecules on the surface of cells that assist leukocytes in interacting with their environments through adherence. In particular, integrins are a group of glycoproteins expressed on both leukocytes and endothelial cells that are predominately involved in the aberrant leukocyte trafficking and extravasation associated with autoimmune diseases. Integrins promote adherence of leukocytes to the surface of endothelial cells on the surface of blood vessels through which leukocytes circulate. Studies have shown that lipid rafts play a role in the regulation of integrin function (Leitinger and Hogg (2002) *J. Cell Sci.* 115: 963-972). Moreover, it is known that  $\alpha 5 \beta 1$  integrin functions can be modulated by the phospholipid and cholesterol contents of cell membranes (Gopalakrishna, et al. (2000) *J. Cell. Biochem.* 77: 517-528). Therefore, it is likely that the aberrant leukocyte trafficking and extravasation which occurs in autoimmune disorders can be inhibited by disrupting lipid raft formation and/or organization in the plasma membrane of leukocytes.

Chemokines are chemoattractant cytokines that mediate chemotaxis of leukocytes involved in autoimmune diseases. Excess levels of these cytokines are linked to autoimmune disorders. The receptors for chemokines are mainly expressed on immune and inflammatory cells, such as T and B lymphocytes, dendritic cells, monocytes/macrophages and granulocytes, in which ligand-receptor interactions lead to cell migration. Chemokine expression is either induced at autoimmune disease sites to recruit T-cells that mediate tissue destruction, or is constitutive in lymphoid organs (i.e., lymph nodes and spleen) to orchestrate the response to antigens, including autoantigens, that drive autoimmune diseases. Studies have indicated that cholesterol (a major component of lipid rafts) is essential for macrophage inflammatory protein 1 $\beta$  binding and conformational integrity of CC chemokine receptor 5 (Nguyen and Taub (2002) *Blood* 99: 4298-4306). This suggests that disrupting lipid rafts in the plasma membranes of immune cells will

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likely have an effect on ligand-chemokine receptor interactions that lead to the chemotaxis of leukocytes associated with autoimmune diseases.

Furthermore, reports have drawn a correlation between cholesterol and the development of rheumatoid arthritis in human populations (Heliovaara, et al. (1996) Br. J. Rheumatology 35: 255-257; Winyard, et al. (1993) Ann. Rheumatic Dis. 52: 677-680). A correlation between cholesterol and rheumatoid arthritis has also been shown in studies with pre-clinical rodent models (Hamer, et al. (2002) J. Cell. Mol. Med. 6: 407-414; Nair, et al. (1998) Eur. J. Oral. Sci. 106: 644-650). Studies have also established an association between plant sterols and arthritis (Bhattacharyya (1984) 136: 32-34; and Bjorkhem and Skrede *In The Metabolic Basis of Inherited Disease*, 6<sup>th</sup> ed. Scriver, et al., eds. McGraw-Hill, New York (1989), pp. 1283-1302). Moreover, a relationship between plant sterols and lymphocyte activation has also been observed (Bouic, et al. (1996) Int. J. Immunopharmacol. 18: 693-700).

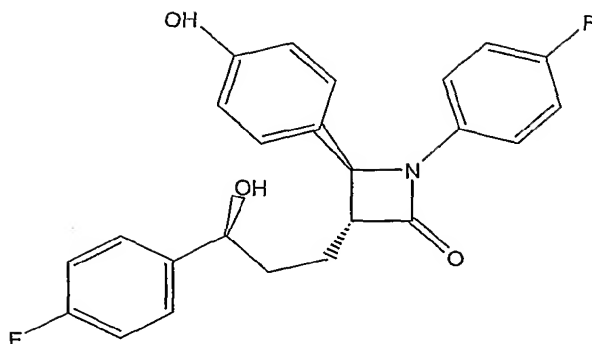
There is a need in the art for compositions and treatments which modulate cholesterol and plant sterol levels for the treatment of autoimmune disorders by disrupting lipid raft formation and organization within the plasma membranes of leukocytes.

#### SUMMARY OF THE INVENTION

In one embodiment, there is provided a method of treating or preventing autoimmune disorder in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof.

A method of treating or preventing an autoimmune disorder in a subject is further provided, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor represented by Formula (II) below:

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(II)

or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the present invention provides a composition comprising: (a) at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof and (b) at least one other agent useful for the treatment of an autoimmune disorder.

Therapeutic combinations also are provided comprising: (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof; and (b) a second amount of at least one other agent useful for the treatment of an autoimmune disorder, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of an autoimmune disorder in a subject.

Pharmaceutical compositions for the treatment or prevention of an autoimmune disorder in a subject, comprising a therapeutically effective amount of the above compounds, compositions or therapeutic combinations and a pharmaceutically acceptable carrier also are provided.

Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about."

#### DETAILED DESCRIPTION

As discussed above, the pathogenesis of autoimmune disorders is mediated by the aberrant activation, differentiation and trafficking of leukocytes in response to

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tissue self-antigens. Autoimmune reactions can often have fatal consequences. They can cause the destruction of vital tissue which manifests in the development of chronic autoimmune diseases. The driving forces in the progression of these diseases are autoreactive immune cells. In most cases, these autoreactive cells are CD4<sup>+</sup> T-cells which somehow escaped the self-tolerance control mechanisms of the immune system. In non-pathogenic situations, CD4<sup>+</sup> T-cells act as T helper cells, which control or mediate the activation and differentiation of other immune cells such as cytotoxic CD8<sup>+</sup> T-cells, NK cells, granulocytes, macrophages and B-cells. However, in the situation of chronic autoimmune diseases, CD4<sup>+</sup> T-cells are no longer just mediators, but are rather key players of the autoimmune response. In particular, they are either directly or indirectly responsible for the characteristic tissue destruction that occurs in autoimmune diseases, which is triggered by the recognition of autoantigens. These autoantigens are derived from self-proteins of the attacked tissue and are presented to the autoreactive CD4<sup>+</sup> T-cells by antigen-presenting cells (APCs), such as macrophages, dendritic cells or B-cells. In addition, aberrant T cell-dependent or T cell-independent antibody production by activated B cells plays a critical role in initiating and amplifying tissue damage in autoimmune disorders.

As described above, the formulation and organization of lipid rafts within the cell membranes of leukocytes has been demonstrated to play a critical role in T-cell and B-cell activation, antigen presentation, adhesion molecule function and chemokine receptor signaling, each of which is associated with the pathogenesis of autoimmune disorders. Both cholesterol and plant sterols have been shown to be essential to the structure and organization of lipid rafts, and to the subsequent downstream signaling events mediated by these rafts. Therefore, depleting the amount of cholesterol trafficked to cells will likely disrupt the formation and organization of lipid rafts in the cell membranes of autoreactive T-cells and other leukocytes involved in autoimmune reactions. When cholesterol absorption in the intestines is reduced by whatever means, less cholesterol is delivered to the liver. The consequence of this action is a decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Mammalian cells acquire a large fraction of their cholesterol by receptor-mediated

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endocytosis of serum lipoproteins, such as LDL. LDL particles carry cholesterol predominantly as cholesteryl esters. Following endocytosis, cholesteryl esters are transported to late endosomes and lysosomes where they are hydrolyzed to release cholesterol for use by the cell as an essential component of the lipid rafts of cell membranes, for example. Thus, any means of reducing the intestinal absorption of cholesterol (and/or plant sterols) will likely disrupt the formation and organization of lipid rafts in the cell membranes of leukocytes involved in autoimmune reactions. Therefore, sterol absorption inhibitors can provide a therapeutically effective method of treating and/or preventing autoimmune disorders.

As used herein, the term "autoimmune disorders" is intended to include any abnormal physical or mental condition, including diseases, which are of an autoimmune etiology, as well as any symptoms which are subject evidence of a disease or disorder.

"Lipid rafts," "raft-like microdomains," and the like as defined herein refer to subdomains within the plasma membrane of many cell types, including leukocytes, which are enriched in cholesterol, sterols derived from plants and sphingolipids. They exist as distinct, liquid-ordered regions of the membrane that are resistant to extraction with non-ionic detergents and exhibit less fluidity than the surrounding plasma membrane due to the presence of cholesterol.

"Leukocytes" as defined herein are white blood cells produced by the immune system to help defend the body against infection. The different types of leukocytes include neutrophils, lymphocytes (e.g. T-cells, B-cells and natural killer (NK cells), monocytes, macrophages, eosinophils, and basophils.

U.S. Patents Nos. 5,767,115, 5,624,920, 5,656,624 and 5,688,787 (each of which is incorporated by reference herein), respectively, disclose hydroxy-substituted azetidinone compounds and substituted  $\beta$ -lactam compounds useful for inhibiting the absorption of cholesterol, thereby lowering cholesterol levels and/or inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Patents Nos. 5,846,966 and 5,661,145 (both incorporated by reference herein), respectively, disclose hydroxy-substituted azetidinone compounds or substituted  $\beta$ -lactam compounds in combination with HMG CoA reductase inhibitors for preventing or



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treating atherosclerosis and reducing plasma cholesterol levels. Such compounds can also be useful in lowering C-reactive protein levels in subjects.

According to the present invention, these and other sterol absorption inhibitors discussed in detail below can be useful in preventing or treating an autoimmune disorder and its associated conditions. Such autoimmune disorders include, but are not limited to, the following: Alopecia Areata, Ankylosing Spondylitis,

Antiphospholipid Syndrome, aplastic anemia, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinemia, pure red cell aplasia, chronic neutropenias, amegakaryocytic thrombocytopenia, antiphospholipid syndromes, autoimmune

thrombocytopenia, autoimmune hemolytic syndromes, antiphospholipid syndromes, autoimmune gastritis, achlorhydria, Autoimmune Addison's Disease, Autoimmune Diabetes, Autoimmune Hemolytic Anemia, Autoimmune Hepatitis, Autoimmune hypophysitis, Autoimmune orchiditis, autoimmune ovarian failure, Behcet's Disease, Bullous Pemphigoid, Cardiomyopathy, Celiac Sprue-Dermatitis, Cicatrical

pemphigoid, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Inflammatory Demyelinating Polyneuropathy, Interstitial cystitis, Churg-Strauss Syndrome, Cicatricial Pemphigoid, CREST Syndrome, Cold Agglutinin Disease, Crohn's Disease, Dermatitis herpetiformis, Discoid Lupus, Drug-induced autoimmune disorders, Endometriosis, Epidermolysis bullosa acquisita, Essential Mixed

Cryoglobulinemia, Fibromyalgia-Fibromyositis, Glomerulonephritis, Good Pasture Syndrome, Graft Versus Host Disease, Graves' Disease, Guillain-Barré, Hashimoto's Thyroiditis, Idiopathic Inflammatory Myopathies, Idiopathic Pulmonary Fibrosis, Idiopathic Thrombocytopenia Purpura (ITP), IgA Nephropathy, Insulin Dependent Diabetes, Juvenile Arthritis, Lichen Planus, Systemic Lupus Erythmatosus ,

Ménière's Disease, Metal-induced autoimmunity disorders, Mixed Connective Tissue Disease, Multiple Sclerosis, Myasthenia Gravis, Myocarditis, Myositis, Optic neuritis, Painless/postpartum thyroiditis, Peripheral nerve vasculitis, Pemphigus Foliaceus, Pemphigus Vulgaris, Pernicious Anemia, Polyarteritis Nodosa, Polychondritis, Polyglandular Syndromes, Polymyalgia Rheumatica, Polymyositis and

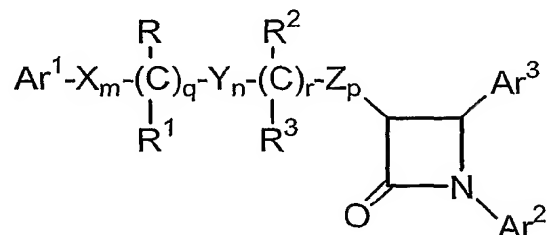
Dermatomyositis, Postinfectious autoimmune disorders, Primary Agammaglobulinemia, Primary Biliary Cirrhosis, Psoriasis, Psoriatic Arthritis, Reactive Arthritis, Raynaud's Phenomenon, Reiter's Syndrome, Rheumatic Fever,

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Rheumatoid Arthritis, Sarcoidosis, Scleritis, Scleroderma, Sjögren's Syndrome, Stiff-Man Syndrome, Takayasu Arteritis, Temporal Arteritis/Giant-cell Arteritis, Ulcerative Colitis, Uveitis, Vasculitis, Vitiligo, and Wegener's Granulomatosis.

In one embodiment, the present invention is directed to compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment using the same comprising at least one (one or more) sterol absorption inhibitor(s). Suitable sterol absorption inhibitors include substituted azetidinone sterol absorption inhibitors, substituted  $\beta$ -lactam sterol absorption inhibitors or combinations thereof as discussed in detail below. As used herein, "sterol absorption inhibitor" means a compound capable of inhibiting the absorption of one or more sterols, including but not limited to, cholesterol and phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol), when administered in a therapeutically effective (sterol absorption inhibiting) amount to a subject, such as a mammal or human.

In a preferred embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (I) below:



(I)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (I) above:

$\text{Ar}^1$  and  $\text{Ar}^2$  are independently selected from the group consisting of aryl and  $\text{R}^4$ -substituted aryl;

$\text{Ar}^3$  is aryl or  $\text{R}^5$ -substituted aryl;

X, Y and Z are independently selected from the group consisting of  $-\text{CH}_2-$ ,  $-\text{CH}(\text{lower alkyl})-$  and  $-\text{C}(\text{dilower alkyl})-$ ;

R and  $\text{R}^2$  are independently selected from the group consisting of  $-\text{OR}^6$ ,

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$-\text{O}(\text{CO})\text{R}^6$ ,  $-\text{O}(\text{CO})\text{OR}^9$  and  $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$ ;

$\text{R}^1$  and  $\text{R}^3$  are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

$q$  is 0 or 1;  $r$  is 0 or 1;  $m$ ,  $n$  and  $p$  are independently selected from 0, 1, 2, 3 or 4; provided that at least one of  $q$  and  $r$  is 1, and the sum of  $m$ ,  $n$ ,  $p$ ,  $q$  and  $r$  is 1, 2, 3, 4, 5 or 6; and provided that when  $p$  is 0 and  $r$  is 1, the sum of  $m$ ,  $q$  and  $n$  is 1, 2, 3, 4 or 5;

$\text{R}^4$  is 1-5 substituents independently selected from the group consisting of lower alkyl,  $-\text{OR}^6$ ,  $-\text{O}(\text{CO})\text{R}^6$ ,  $-\text{O}(\text{CO})\text{OR}^9$ ,  $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$ ,  $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$ ,  $-\text{NR}^6\text{R}^7$ ,  $-\text{NR}^6(\text{CO})\text{R}^7$ ,  $-\text{NR}^6(\text{CO})\text{OR}^9$ ,  $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$ ,  $-\text{NR}^6\text{SO}_2\text{R}^9$ ,  $-\text{COOR}^6$ ,  $-\text{CONR}^6\text{R}^7$ ,  $-\text{COR}^6$ ,  $-\text{SO}_2\text{NR}^6\text{R}^7$ ,  $\text{S}(\text{O})_{0-2}\text{R}^9$ ,  $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$ ,  $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$ ,  $-(\text{lower alkylene})\text{COOR}^6$ ,  $-\text{CH}=\text{CH}-\text{COOR}^6$ ,  $-\text{CF}_3$ ,  $-\text{CN}$ ,  $-\text{NO}_2$  and halogen;

$\text{R}^5$  is 1-5 substituents independently selected from the group consisting of  $-\text{OR}^6$ ,  $-\text{O}(\text{CO})\text{R}^6$ ,  $-\text{O}(\text{CO})\text{OR}^9$ ,  $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$ ,  $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$ ,  $-\text{NR}^6\text{R}^7$ ,  $-\text{NR}^6(\text{CO})\text{R}^7$ ,  $-\text{NR}^6(\text{CO})\text{OR}^9$ ,  $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$ ,  $-\text{NR}^6\text{SO}_2\text{R}^9$ ,  $-\text{COOR}^6$ ,  $-\text{CONR}^6\text{R}^7$ ,  $-\text{COR}^6$ ,  $-\text{SO}_2\text{NR}^6\text{R}^7$ ,  $\text{S}(\text{O})_{0-2}\text{R}^9$ ,  $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$ ,  $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$ ,  $-(\text{lower alkylene})\text{COOR}^6$  and  $-\text{CH}=\text{CH}-\text{COOR}^6$ ;

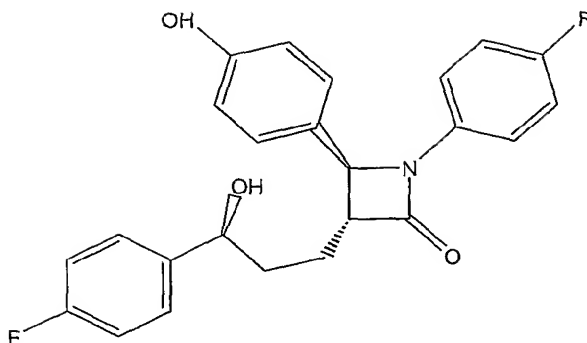
$\text{R}^6$ ,  $\text{R}^7$  and  $\text{R}^8$  are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

$\text{R}^9$  is lower alkyl, aryl or aryl-substituted lower alkyl.

Preferably,  $\text{R}^4$  is 1-3 independently selected substituents, and  $\text{R}^5$  is preferably 1-3 independently selected substituents.

In a preferred embodiment, a sterol absorption inhibitor of Formula (I) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (II) (ezetimibe) below:

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(II)

or a pharmaceutically acceptable salt or solvate thereof. The compound of Formula (II) can be in anhydrous or hydrated form. The compound of Formula (II) is commercially available in a pharmaceutical formulation ZETIA<sup>®</sup> from MSP Pharmaceuticals, Inc.

As used herein, the term "alkyl" or "lower alkyl" means straight or branched alkyl chains having from 1 to 6 carbon atoms and "alkoxy" means alkoxy groups having 1 to 6 carbon atoms. Non-limiting examples of lower alkyl groups include, for example methyl, ethyl, propyl, and butyl groups. Where an alkyl chain joins two other variables and is therefore bivalent, the term alkylene is used.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms, such as phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

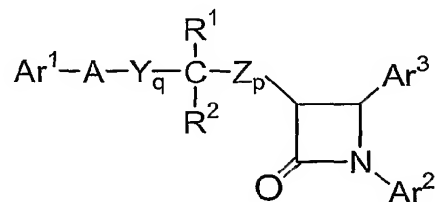
The statements wherein, for example, R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are said to be independently selected from a group of substituents mean that R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently selected, but also that where an R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> variable occurs more than once in a molecule, each occurrence is independently selected (e.g., if R is -OR<sup>6</sup>, wherein R<sup>6</sup> is hydrogen, R<sup>2</sup> can be -OR<sup>6</sup> wherein R<sup>6</sup> is lower alkyl). Those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents that can be present.

Compounds of Formula I can be prepared by a variety of methods well known to those skilled in the art, for example such as are disclosed in U.S. Patents Nos. 5,631,365, 5,767,115, 5,846,966, 6,207,822, PCT Patent Application No. 02/079174

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and PCT Patent Application WO 93/02048, each of which is incorporated herein by reference, and in the Example below.

Alternative sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (III) below:



(III)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (III) above:

Ar<sup>1</sup> is R<sup>3</sup>-substituted aryl;

Ar<sup>2</sup> is R<sup>4</sup>-substituted aryl;

Ar<sup>3</sup> is R<sup>5</sup>-substituted aryl;

Y and Z are independently selected from the group consisting of -CH<sub>2</sub>-, -CH(lower alkyl)- and -C(dilower alkyl)-;

A is selected from -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-;

R<sup>1</sup> is selected from the group consisting of -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup> and -O(CO)NR<sup>6</sup>R<sup>7</sup>; R<sup>2</sup> is selected from the group consisting of hydrogen, lower alkyl and aryl; or R<sup>1</sup> and R<sup>2</sup> together are =O;

q is 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

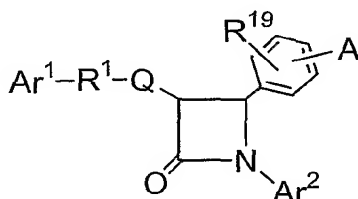
R<sup>5</sup> is 1-3 substituents independently selected from the group consisting of -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>9</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>-lower alkyl, -NR<sup>6</sup>SO<sub>2</sub>-aryl, -CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, S(O)<sub>0-2</sub>-alkyl, S(O)<sub>0-2</sub>-aryl, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-COOR<sup>6</sup>, and -CH=CH-COOR<sup>6</sup>;

$R^3$  and  $R^4$  are independently 1-3 substituents independently selected from the group consisting of  $R^5$ , hydrogen, p-lower alkyl, aryl,  $-\text{NO}_2$ ,  $-\text{CF}_3$  and p-halogeno;

$R^6$ ,  $R^7$  and  $R^8$  are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and  $R^9$  is lower alkyl, aryl or aryl-substituted lower alkyl.

Methods for making compounds of Formula III are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,688,990, which is incorporated herein by reference.

In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (IV) above:

A is selected from the group consisting of  $R^2$ -substituted heterocycloalkyl,  $R^2$ -substituted heteroaryl,  $R^2$ -substituted benzofused heterocycloalkyl, and  $R^2$ -substituted benzofused heteroaryl;

$\text{Ar}^1$  is aryl or  $R^3$ -substituted aryl;

$\text{Ar}^2$  is aryl or  $R^4$ -substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the

spiro group ; and

$R^1$  is selected from the group consisting of:

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-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

-(CH<sub>2</sub>)<sub>e</sub>-G-(CH<sub>2</sub>)<sub>r</sub>-, wherein G is -O-, -C(O)-, phenylene, -NR<sup>8</sup>- or -S(O)<sub>0-2</sub>-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

5 -(C<sub>2</sub>-C<sub>6</sub> alkenylene)-; and

-(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R<sup>5</sup> is selected from:

$\begin{array}{c} | \\ -\text{CH}- \\ | \end{array}$ ,  $\begin{array}{c} | \\ -\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})- \\ | \end{array}$ ,  $\begin{array}{c} | \\ -\text{CF}- \\ | \end{array}$ ,  $\begin{array}{c} | \\ -\text{C}(\text{OH})- \\ | \end{array}$ ,  $\begin{array}{c} | \\ -\text{C}(\text{C}_6\text{H}_4\text{-R}^9)- \\ | \end{array}$ ,  $\begin{array}{c} | \\ -\text{N}- \\ | \end{array}$ , or  $\begin{array}{c} | \\ -\text{N}^+\text{O}^- \\ | \end{array}$ ;

10 R<sup>6</sup> and R<sup>7</sup> are independently selected from the group consisting of -CH<sub>2</sub>-, -CH(C<sub>1</sub>-C<sub>6</sub> alkyl)-, -C(di-(C<sub>1</sub>-C<sub>6</sub>) alkyl)-, -CH=CH- and -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-; or R<sup>5</sup> together with an adjacent R<sup>6</sup>, or R<sup>5</sup> together with an adjacent R<sup>7</sup>, form a -CH=CH- or a -CH=C(C<sub>1</sub>-C<sub>6</sub> alkyl)- group;

15 a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R<sup>6</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, a is 1; provided that when R<sup>7</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R<sup>6</sup>'s can be the same or different; and provided that when b is 2 or 3, the R<sup>7</sup>'s can be the same or different;

and when Q is a bond, R<sup>1</sup> also can be selected from:

20  $\begin{array}{c} \text{R}^{10} \\ | \\ -\text{M}-\text{Y}_d-\text{C}-\text{Z}_h- \\ | \\ \text{R}^{11} \end{array}$ ,  $\begin{array}{c} \text{R}^{12} \\ | \\ -\text{X}_m-(\text{C})_s-\text{Y}_n-(\text{C})_t-\text{Z}_p- \\ | \quad | \\ \text{R}^{13} \quad \text{R}^{11} \end{array}$  or  $\begin{array}{c} \text{R}^{10} \\ | \\ -\text{X}_j-(\text{C})_v-\text{Y}_k-\text{S}(\text{O})_{0-2}- \\ | \\ \text{R}^{11} \end{array}$ ;

where M is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-;

X, Y and Z are independently selected from the group consisting of -CH<sub>2</sub>-, -CH(C<sub>1</sub>-C<sub>6</sub> alkyl)- and -C(di-(C<sub>1</sub>-C<sub>6</sub>) alkyl)-;

25 R<sup>10</sup> and R<sup>12</sup> are independently selected from the group consisting of -OR<sup>14</sup>, -O(CO)R<sup>14</sup>, -O(CO)OR<sup>16</sup> and -O(CO)NR<sup>14</sup>R<sup>15</sup>;

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$R^{11}$  and  $R^{13}$  are independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl and aryl; or  $R^{10}$  and  $R^{11}$  together are  $=O$ , or  $R^{12}$  and  $R^{13}$  together are  $=O$ ;

d is 1, 2 or 3;

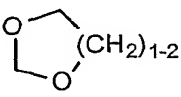
h is 0, 1, 2, 3 or 4;

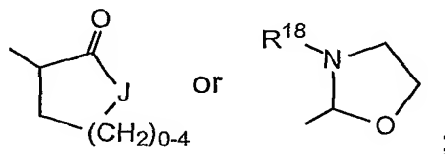
s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

$R^2$  is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl,  $(C_3-C_6)$ cycloalkyl,  $(C_3-C_6)$ cycloalkenyl,  $R^{17}$ -substituted aryl,  $R^{17}$ -substituted benzyl,  $R^{17}$ -substituted benzyloxy,  $R^{17}$ -substituted aryloxy, halogeno,  $-NR^{14}R^{15}$ ,  $NR^{14}R^{15}(C_1-C_6 \text{ alkylene})-$ ,  $NR^{14}R^{15}C(O)(C_1-C_6 \text{ alkylene})-$ ,  $-NHC(O)R^{16}$ , OH,  $C_1-C_6$  alkoxy,  $-OC(O)R^{16}$ ,  $-COR^{14}$ , hydroxy $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy $(C_1-C_6)$ alkyl,  $NO_2$ ,  $-S(O)_{0-2}R^{16}$ ,  $-SO_2NR^{14}R^{15}$  and  $-(C_1-C_6 \text{ alkylene})COOR^{14}$ ; when  $R^2$  is a substituent on a

heterocycloalkyl ring,  $R^2$  is as defined, or is  $=O$  or ; and, where  $R^2$  is a substituent on a substitutable ring nitrogen, it is hydrogen,  $(C_1-C_6)$ alkyl, aryl,  $(C_1-C_6)$ alkoxy, aryloxy,  $(C_1-C_6)$ alkylcarbonyl, arylcarbonyl, hydroxy,  $-(CH_2)_{1-6}CONR^{18}R^{18}$ ,



wherein J is  $-O-$ ,  $-NH-$ ,  $-NR^{18}-$  or  $-CH_2-$ ;



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$R^3$  and  $R^4$  are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of  $(C_1-C_6)$ alkyl,  $-OR^{14}$ ,  $-O(CO)R^{14}$ ,  $-O(CO)OR^{16}$ ,  $-O(CH_2)_{1-5}OR^{14}$ ,  $-O(CO)NR^{14}R^{15}$ ,  $-NR^{14}R^{15}$ ,  $-NR^{14}(CO)R^{15}$ ,  $-NR^{14}(CO)OR^{16}$ ,  $-NR^{14}(CO)NR^{15}R^{19}$ ,  $-NR^{14}SO_2R^{16}$ ,  $-COOR^{14}$ ,  $-CONR^{14}R^{15}$ ,  $-COR^{14}$ ,  $-SO_2NR^{14}R^{15}$ ,  $S(O)_{0-2}R^{16}$ ,  $-O(CH_2)_{1-10}-COOR^{14}$ ,  $-O(CH_2)_{1-10}CONR^{14}R^{15}$ ,  $-(C_1-C_6 \text{ alkylene})-COOR^{14}$ ,  $-CH=CH-COOR^{14}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$  and halogen;

$R^8$  is hydrogen,  $(C_1-C_6)$ alkyl, aryl  $(C_1-C_6)$ alkyl,  $-C(O)R^{14}$  or  $-COOR^{14}$ ;

$R^9$  and  $R^{17}$  are independently 1-3 groups independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy,  $-COOH$ ,  $NO_2$ ,  $-NR^{14}R^{15}$ ,  $OH$  and halogeno;

$R^{14}$  and  $R^{15}$  are independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl, aryl and aryl-substituted  $(C_1-C_6)$ alkyl;

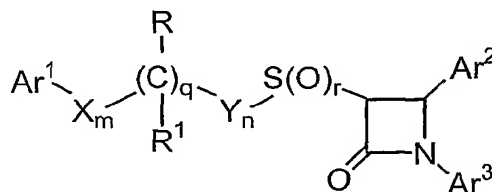
$R^{16}$  is  $(C_1-C_6)$ alkyl, aryl or  $R^{17}$ -substituted aryl;

$R^{18}$  is hydrogen or  $(C_1-C_6)$ alkyl; and

$R^{19}$  is hydrogen, hydroxy or  $(C_1-C_6)$ alkoxy.

Methods for making compounds of Formula IV are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,656,624, which is incorporated herein by reference.

In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):



(V)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (V) above:

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Ar<sup>1</sup> is aryl, R<sup>10</sup>-substituted aryl or heteroaryl;

Ar<sup>2</sup> is aryl or R<sup>4</sup>-substituted aryl;

Ar<sup>3</sup> is aryl or R<sup>5</sup>-substituted aryl;

X and Y are independently selected from the group consisting of -CH<sub>2</sub>-,

5 -CH(lower alkyl)- and -C(dilower alkyl)-;

R is -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup> or -O(CO)NR<sup>6</sup>R<sup>7</sup>; R<sup>1</sup> is hydrogen, lower alkyl or aryl; or R and R<sup>1</sup> together are =O;

q is 0 or 1;

r is 0, 1 or 2;

10 m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

R<sup>4</sup> is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>6</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>R<sup>9</sup>, -COOR<sup>6</sup>,  
15 -CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, S(O)<sub>0-2</sub>R<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>, -(lower alkylene)COOR<sup>6</sup> and -CH=CH-COOR<sup>6</sup>;

R<sup>5</sup> is 1-5 substituents independently selected from the group consisting of -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>6</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>R<sup>9</sup>, -COOR<sup>6</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -  
20 SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, S(O)<sub>0-2</sub>R<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, halogen, -(lower alkylene)COOR<sup>6</sup> and -CH=CH-COOR<sup>6</sup>;

R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

25 R<sup>9</sup> is lower alkyl, aryl or aryl-substituted lower alkyl; and

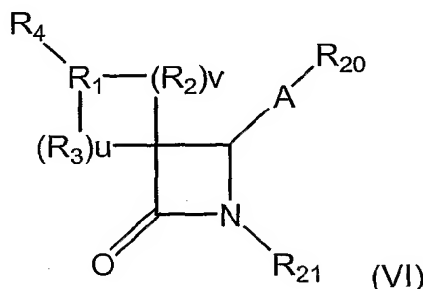
R<sup>10</sup> is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>6</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>R<sup>9</sup>, -COOR<sup>6</sup>,

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-CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, -S(O)<sub>0-2</sub>R<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>,  
-CF<sub>3</sub>, -CN, -NO<sub>2</sub> and halogen.

Methods for making compounds of Formula V are well known to those skilled  
in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent  
No. 5,624,920, which is incorporated herein by reference.

In another embodiment, sterol absorption inhibitors useful in the compositions,  
therapeutic combinations and methods of the present invention are represented by  
Formula (VI):



or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein:

R<sub>1</sub> is

-CH-, -C(lower alkyl)-, -CF-, -C(OH)-, -C(C<sub>6</sub>H<sub>5</sub>)-, -C(C<sub>6</sub>H<sub>4</sub>-R<sub>15</sub>)-,  
-N<sup>+</sup> or -N<sup>+</sup>O<sup>-</sup> ;

R<sub>2</sub> and R<sub>3</sub> are independently selected from the group consisting of:  
-CH<sub>2</sub>-, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower alkyl)=CH-; or  
R<sub>1</sub> together with an adjacent R<sub>2</sub>, or R<sub>1</sub> together with an adjacent R<sub>3</sub>, form a  
-CH=CH- or a -CH=C(lower alkyl)- group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided  
that when R<sub>2</sub> is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R<sub>3</sub> is  
-CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R<sub>2</sub>'s can  
be the same or different; and provided that when u is 2 or 3, the R<sub>3</sub>'s can be the  
same or different;

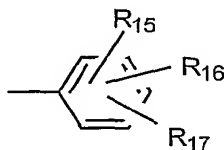
R<sub>4</sub> is selected from B-(CH<sub>2</sub>)<sub>m</sub>C(O)-, wherein m is 0, 1, 2, 3, 4 or 5;

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B-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 0, 1, 2, 3, 4, 5 or 6; B-(CH<sub>2</sub>)<sub>e</sub>-Z-(CH<sub>2</sub>)<sub>r</sub>-, wherein Z is -O-,  
 -C(O)-, phenylene, -N(R<sub>8</sub>)- or -S(O)<sub>0-2</sub>-, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or  
 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6; B-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-; B-  
 (C<sub>4</sub>-C<sub>6</sub> alkadienylene)-; B-(CH<sub>2</sub>)<sub>t</sub>-Z-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-, wherein Z is as defined  
 5 above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of  
 carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; B-(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein  
 V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that  
 the sum of f and g is 1, 2, 3, 4, 5 or 6; B-(CH<sub>2</sub>)<sub>t</sub>-V-(C<sub>2</sub>-C<sub>6</sub> alkenylene)- or B-(C<sub>2</sub>-C<sub>6</sub>  
 alkenylene)-V-(CH<sub>2</sub>)<sub>t</sub>-, wherein V and t are as defined above, provided that the sum  
 10 of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;  
 B-(CH<sub>2</sub>)<sub>a</sub>-Z-(CH<sub>2</sub>)<sub>b</sub>-V-(CH<sub>2</sub>)<sub>d</sub>-, wherein Z and V are as defined above and a, b and  
 d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2,  
 3, 4, 5 or 6; or T-(CH<sub>2</sub>)<sub>s</sub>-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1,  
 2, 3, 4, 5 or 6; or

15 R<sub>1</sub> and R<sub>4</sub> together form the group  $\text{B}-\text{CH}=\overset{\text{I}}{\text{C}}-$ ;

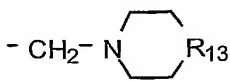
B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or  
 W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of  
 pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl,  
 thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides  
 20 thereof, or



W is 1 to 3 substituents independently selected from the group consisting of  
 lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy,  
 alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl  
 25 lower alkanedioyl, allyloxy, -CF<sub>3</sub>, -OCF<sub>3</sub>, benzyl, R<sub>7</sub>-benzyl, benzyloxy, R<sub>7</sub>-  
 benzyloxy, phenoxy, R<sub>7</sub>-phenoxy, dioxolanyl, NO<sub>2</sub>, -N(R<sub>8</sub>)(R<sub>9</sub>), N(R<sub>8</sub>)(R<sub>9</sub>)-lower  
 alkylene-, N(R<sub>8</sub>)(R<sub>9</sub>)-lower alkylenyloxy-, OH, halogeno, -CN, -N<sub>3</sub>, -NHC(O)OR<sub>10</sub>,

- 20 -

-NHC(O)R<sub>10</sub>, R<sub>11</sub>O<sub>2</sub>SNH-, (R<sub>11</sub>O<sub>2</sub>S)<sub>2</sub>N-, -S(O)<sub>2</sub>NH<sub>2</sub>, -S(O)<sub>0-2</sub>R<sub>8</sub>, tert-butyl-dimethyl-silyloxymethyl, -C(O)R<sub>12</sub>, -COOR<sub>19</sub>, -CON(R<sub>8</sub>)(R<sub>9</sub>), -CH=CHC(O)R<sub>12</sub>, -lower alkylene-C(O)R<sub>12</sub>, R<sub>10</sub>C(O)(lower alkyleneoxy)-,

N(R<sub>8</sub>)(R<sub>9</sub>)C(O)(lower alkyleneoxy)- and  for substitution on ring carbon atoms,

and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR<sub>10</sub>, -C(O)R<sub>10</sub>, OH, N(R<sub>8</sub>)(R<sub>9</sub>)-lower alkylene-, N(R<sub>8</sub>)(R<sub>9</sub>)-lower alkyleneoxy-, -S(O)<sub>2</sub>NH<sub>2</sub> and 2-(trimethylsilyl)-ethoxymethyl;

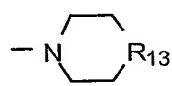
R<sub>7</sub> is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO<sub>2</sub>, -N(R<sub>8</sub>)(R<sub>9</sub>), OH, and halogeno;

R<sub>8</sub> and R<sub>9</sub> are independently selected from H or lower alkyl;

R<sub>10</sub> is selected from lower alkyl, phenyl, R<sub>7</sub>-phenyl, benzyl or R<sub>7</sub>-benzyl;

R<sub>11</sub> is selected from OH, lower alkyl, phenyl, benzyl, R<sub>7</sub>-phenyl or R<sub>7</sub>-benzyl;

R<sub>12</sub> is selected from H, OH, alkoxy, phenoxy, benzyloxy,

, -N(R<sub>8</sub>)(R<sub>9</sub>), lower alkyl, phenyl or R<sub>7</sub>-phenyl;

R<sub>13</sub> is selected from -O-, -CH<sub>2</sub>-, -NH-, -N(lower alkyl)- or -NC(O)R<sub>19</sub>;

R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub> are independently selected from the group consisting of H and the groups defined for W; or R<sub>15</sub> is hydrogen and R<sub>16</sub> and R<sub>17</sub>, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R<sub>19</sub> is H, lower alkyl, phenyl or phenyl lower alkyl; and

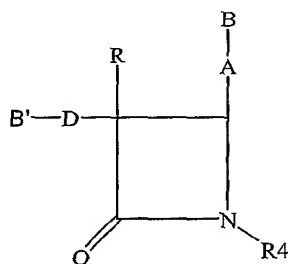
R<sub>20</sub> and R<sub>21</sub> are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused

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heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

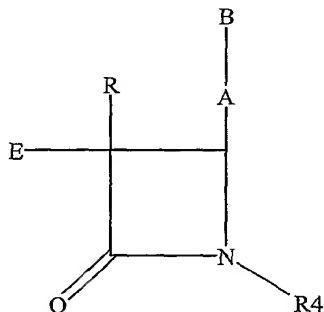
Methods for making compounds of Formula VI are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,698,548, which is incorporated herein by reference.

In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formulas (VIIA) and (VIIB):



(VIIA)

and



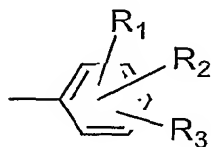
(VIIB)

or a pharmaceutically acceptable salt or solvate thereof,

wherein:

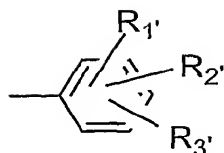
A is  $-\text{CH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$  or  $-(\text{CH}_2)_p-$  wherein p is 0, 1 or 2;

B is



B' is

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D is  $-(CH_2)_mC(O)-$  or  $-(CH_2)_q-$  wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

E is C<sub>10</sub> to C<sub>20</sub> alkyl or  $-C(O)-(C_9 \text{ to } C_{19})\text{-alkyl}$ , wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

R is hydrogen, C<sub>1</sub>-C<sub>15</sub> alkyl, straight or branched, saturated or containing one or more double bonds, or  $B-(CH_2)_r-$ , wherein r is 0, 1, 2, or 3;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>1'</sub>, R<sub>2'</sub>, and R<sub>3'</sub> are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO<sub>2</sub>, NH<sub>2</sub>, OH, halogeno, lower alkylamino, dilower alkylamino,  $-NHC(O)OR_5$ ,  $R_6O_2SNH-$  and  $-S(O)_2NH_2$ ;

R<sub>4</sub> is

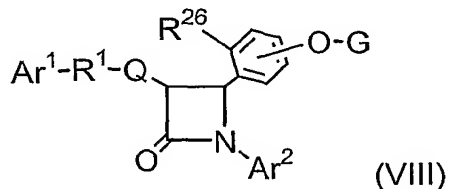


wherein n is 0, 1, 2 or 3;

R<sub>5</sub> is lower alkyl; and

R<sub>6</sub> is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO<sub>2</sub>, NH<sub>2</sub>, OH, halogeno, lower alkylamino and dilower alkylamino; or a pharmaceutically acceptable salt thereof or a solvate thereof.

In another embodiment, sterol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (VIII):

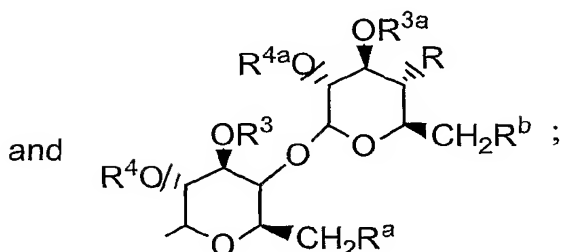
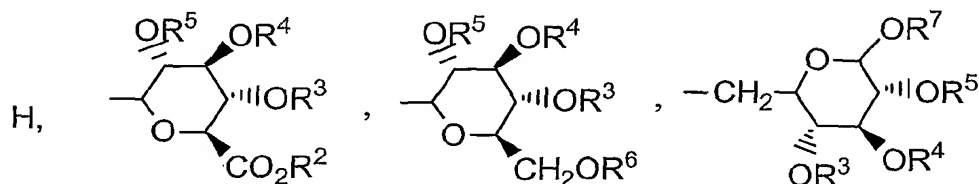


or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (VIII) above,

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R<sup>26</sup> is H or OG<sup>1</sup>;

G and G<sup>1</sup> are independently selected from the group consisting of



provided that when R<sup>26</sup> is H or

OH, G is not H;

R, R<sup>a</sup> and R<sup>b</sup> are independently selected from the group consisting of H, -OH, halogeno, -NH<sub>2</sub>, azido, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)-alkoxy or -W-R<sup>30</sup>;

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R<sup>31</sup>)-, -NH-C(O)-N(R<sup>31</sup>)- and -O-C(S)-N(R<sup>31</sup>)-;

R<sup>2</sup> and R<sup>6</sup> are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup>, R<sup>3a</sup> and R<sup>4a</sup> are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl and -C(O)aryl;

R<sup>30</sup> is selected from the group consisting of R<sup>32</sup>-substituted T, R<sup>32</sup>-substituted-T-(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sup>32</sup>-substituted-(C<sub>2</sub>-C<sub>4</sub>)alkenyl, R<sup>32</sup>-substituted-(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sup>32</sup>-substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl and R<sup>32</sup>-substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>31</sup> is selected from the group consisting of H and (C<sub>1</sub>-C<sub>4</sub>)alkyl;

T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;



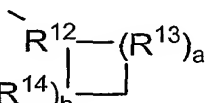
- 24 -

R<sup>32</sup> is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH, phenoxy, -CF<sub>3</sub>, -NO<sub>2</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, methylenedioxy, oxo, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfanyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, -N(CH<sub>3</sub>)<sub>2</sub>, -C(O)-NH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -C(O)-N((C<sub>1</sub>-C<sub>4</sub>)alkyl)<sub>2</sub>, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkoxy and pyrrolidinylcarbonyl; or R<sup>32</sup> is a covalent bond and R<sup>31</sup>, the nitrogen to which it is attached and R<sup>32</sup> form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyll or morpholinyll group, or a (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyll or morpholinyll group;

Ar<sup>1</sup> is aryl or R<sup>10</sup>-substituted aryl;

Ar<sup>2</sup> is aryl or R<sup>11</sup>-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone,

forms the spiro group ; and

R<sup>1</sup> is selected from the group consisting of

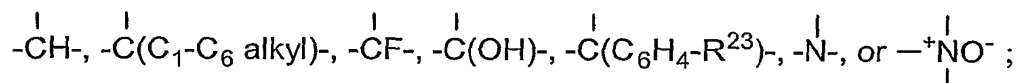






-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

-(CH<sub>2</sub>)<sub>e</sub>-E-(CH<sub>2</sub>)<sub>r</sub>-, wherein E is -O-, -C(O)-, phenylene, -NR<sup>22</sup>- or -S(O)<sub>0-2</sub>-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-(C<sub>2</sub>-C<sub>6</sub>)alkenylene-; and

-(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R<sup>12</sup> is

-CH-, -C(C<sub>1</sub>-C<sub>6</sub> alkyl)-, -CF-, -C(OH)-, -C(C<sub>6</sub>H<sub>4</sub>-R<sup>23</sup>)-, -N-, or -<sup>+</sup>NO<sup>-</sup>;

R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of

-CH<sub>2</sub>-, -CH(C<sub>1</sub>-C<sub>6</sub> alkyl)-, -C(di-(C<sub>1</sub>-C<sub>6</sub>) alkyl)-, -CH=CH- and

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-C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-; or R<sup>12</sup> together with an adjacent R<sup>13</sup>, or R<sup>12</sup> together with an adjacent R<sup>14</sup>, form a -CH=CH- or a -CH=C(C<sub>1</sub>-C<sub>6</sub> alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero;

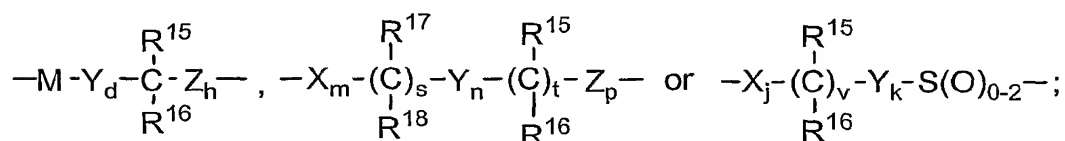
provided that when R<sup>13</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, a is 1;

5 provided that when R<sup>14</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, b is 1;

provided that when a is 2 or 3, the R<sup>13</sup>'s can be the same or different; and

provided that when b is 2 or 3, the R<sup>14</sup>'s can be the same or different;

and when Q is a bond, R<sup>1</sup> also can be:



10 M is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-;

X, Y and Z are independently selected from the group consisting of -CH<sub>2</sub>-, -CH(C<sub>1</sub>-C<sub>6</sub>)alkyl- and -C(di-(C<sub>1</sub>-C<sub>6</sub>)alkyl);

R<sup>10</sup> and R<sup>11</sup> are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of

15 (C<sub>1</sub>-C<sub>6</sub>)alkyl, -OR<sup>19</sup>, -O(CO)R<sup>19</sup>, -O(CO)OR<sup>21</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>19</sup>,

-O(CO)NR<sup>19</sup>R<sup>20</sup>, -NR<sup>19</sup>R<sup>20</sup>, -NR<sup>19</sup>(CO)R<sup>20</sup>, -NR<sup>19</sup>(CO)OR<sup>21</sup>,

-NR<sup>19</sup>(CO)NR<sup>20</sup>R<sup>25</sup>, -NR<sup>19</sup>SO<sub>2</sub>R<sup>21</sup>, -COOR<sup>19</sup>, -CONR<sup>19</sup>R<sup>20</sup>, -COR<sup>19</sup>,

-SO<sub>2</sub>NR<sup>19</sup>R<sup>20</sup>, S(O)<sub>0-2</sub>R<sup>21</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>19</sup>,

-O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>19</sup>R<sup>20</sup>, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-COOR<sup>19</sup>, -CH=CH-COOR<sup>19</sup>,

20 -CF<sub>3</sub>, -CN, -NO<sub>2</sub> and halogen;

R<sup>15</sup> and R<sup>17</sup> are independently selected from the group consisting of -OR<sup>19</sup>, -O(CO)R<sup>19</sup>, -O(CO)OR<sup>21</sup> and -O(CO)NR<sup>19</sup>R<sup>20</sup>;

R<sup>16</sup> and R<sup>18</sup> are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl and aryl; or R<sup>15</sup> and R<sup>16</sup> together are =O, or R<sup>17</sup> and R<sup>18</sup> together are =O;

d is 1, 2 or 3;

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h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4;

provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and

5 provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

and when Q is a bond and R<sup>1</sup> is 
$$\begin{array}{c} \text{R}^{15} \\ | \\ -\text{X}_j-(\text{C})_v-\text{Y}_k-\text{S}(\text{O})_{0-2}- \\ | \\ \text{R}^{16} \end{array}$$
, Ar<sup>1</sup> can also be  
pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl,  
10 pyrimidinyl or pyridazinyl;

R<sup>19</sup> and R<sup>20</sup> are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and aryl-substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>21</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl or R<sup>24</sup>-substituted aryl;

R<sup>22</sup> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)R<sup>19</sup> or -COOR<sup>19</sup>;

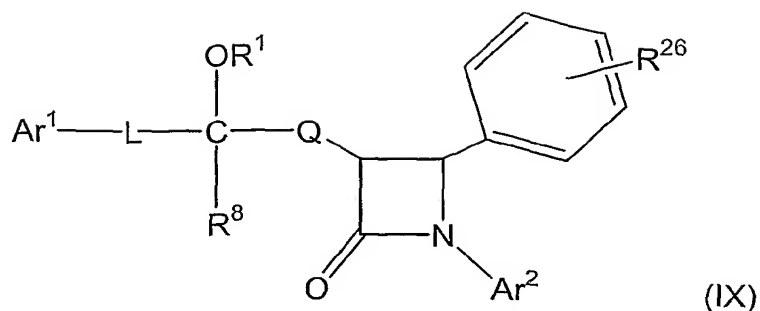
15 R<sup>23</sup> and R<sup>24</sup> are independently 1-3 groups independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, -COOH, NO<sub>2</sub>, -NR<sup>19</sup>R<sup>20</sup>, -OH and halogeno; and

R<sup>25</sup> is H, -OH or (C<sub>1</sub>-C<sub>6</sub>)alkoxy.

20 Methods for making compounds of Formula VIII are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,756,470, which is incorporated herein by reference.

In another embodiment, sterol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (IX) below:

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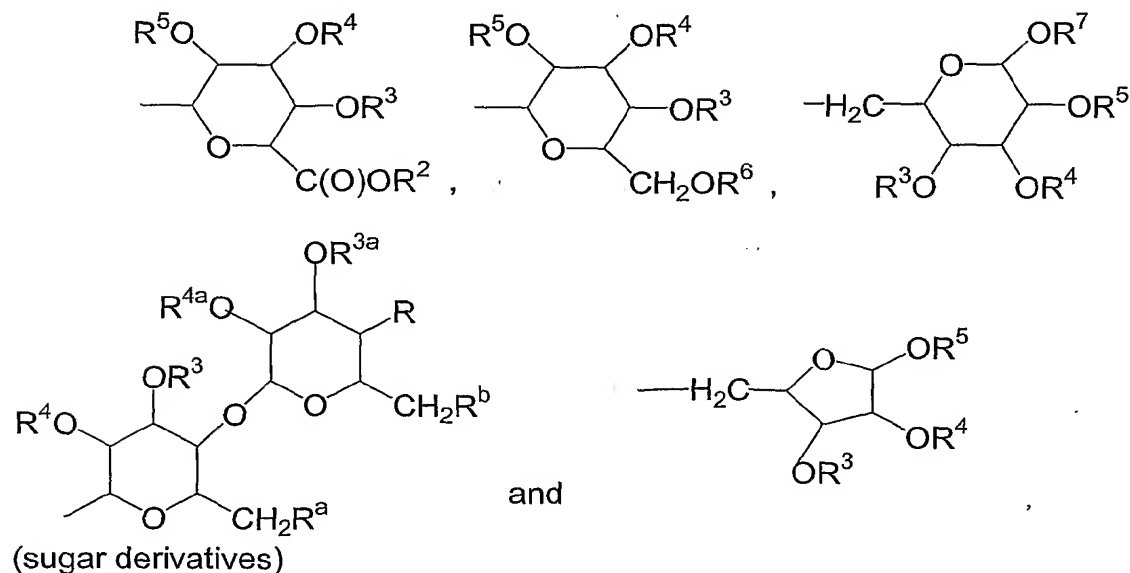


or a pharmaceutically acceptable salt or solvate thereof, wherein in Formula (IX):

$R^1$  is selected from the group consisting of H, G,  $G^1$ ,  $G^2$ ,  $-SO_3H$  and  $-PO_3H$ ;

G is selected from the group consisting of: H,

5



wherein R,  $R^a$  and  $R^b$  are each independently selected from the group consisting of H,  $-OH$ , halo,  $-NH_2$ , azido, (C1-C6)alkoxy(C1-C6)alkoxy or  $-W-R^{30}$ ;

W is independently selected from the group consisting of

10  $-NH-C(O)-$ ,  $-O-C(O)-$ ,  $-O-C(O)-N(R^{31})-$ ,  $-NH-C(O)-N(R^{31})-$  and  $-O-C(S)-N(R^{31})-$ ;

$R^2$  and  $R^6$  are each independently selected from the group consisting of H, (C1-C6)alkyl, acetyl, aryl and aryl(C1-C6)alkyl;

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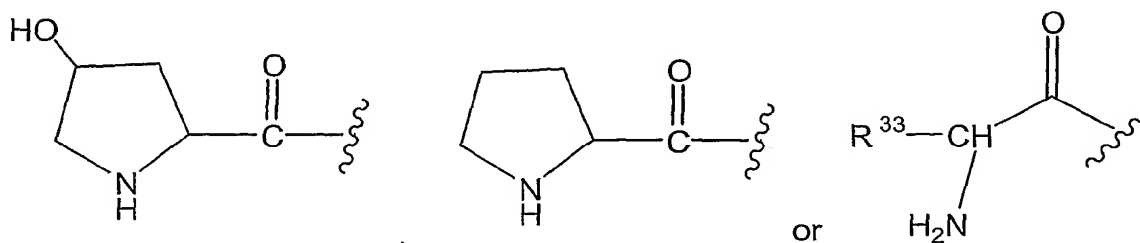
$R^3$ ,  $R^4$ ,  $R^5$ ,  $R^7$ ,  $R^{3a}$  and  $R^{4a}$  are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, acetyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl and -C(O)aryl;

$R^{30}$  is independently selected from the group consisting of  
 5  $R^{32}$ -substituted T,  $R^{32}$ -substituted-T-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  $R^{32}$ -substituted-(C<sub>2</sub>-C<sub>4</sub>)alkenyl,  $R^{32}$ -substituted-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  $R^{32}$ -substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl and  $R^{32}$ -substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

$R^{31}$  is independently selected from the group consisting of H and (C<sub>1</sub>-C<sub>4</sub>)alkyl;

10 T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

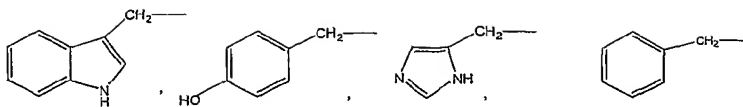
$R^{32}$  is independently selected from 1-3 substituents which are each independently selected from the group consisting of H, halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH,  
 15 phenoxy, -CF<sub>3</sub>, -NO<sub>2</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, methylenedioxy, oxo, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfanyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, -N(CH<sub>3</sub>)<sub>2</sub>, -C(O)-NH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -C(O)-N((C<sub>1</sub>-C<sub>4</sub>)alkyl)<sub>2</sub>, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkoxy and pyrrolidinylcarbonyl;  
 or  $R^{32}$  is a covalent bond and  $R^{31}$ , the nitrogen to which it is attached and  $R^{32}$  form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indoliny or morpholiny group, or a  
 20 (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indoliny or morpholiny group;



$G^1$  is represented by the structure:

wherein  $R^{33}$  is independently selected from the group consisting of unsubstituted alkyl,  $R^{34}$ -substituted alkyl, ( $R^{35}$ )( $R^{36}$ )alkyl-,

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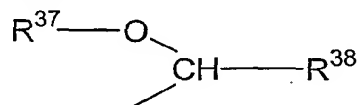


$R^{34}$  is one to three substituents, each  $R^{34}$  being independently selected from the group consisting of  $\text{HOOC-}$ ,  $\text{HO-}$ ,  $\text{HS-}$ ,  $(\text{CH}_3)\text{S-}$ ,  $\text{H}_2\text{N-}$ ,  $(\text{NH}_2)(\text{NH})\text{C}(\text{NH})\text{-}$ ,  $(\text{NH}_2)\text{C}(\text{O})\text{-}$  and  $\text{HOOCCH}(\text{NH}_2^+)\text{CH}_2\text{SS-}$ ;

$R^{35}$  is independently selected from the group consisting of H and  $\text{NH}_2\text{-}$ ;

$R^{36}$  is independently selected from the group consisting of H, unsubstituted alkyl,  $R^{34}$ -substituted alkyl, unsubstituted cycloalkyl and  $R^{34}$ -substituted cycloalkyl;

$G^2$  is represented by the structure:



wherein  $R^{37}$  and  $R^{38}$  are each independently selected from the group consisting of  $(\text{C}_1\text{-C}_6)\text{alkyl}$  and aryl;

$R^{26}$  is one to five substituents, each  $R^{26}$  being independently selected from the group consisting of:

- a) H;
- b)  $\text{-OH}$ ;
- c)  $\text{-OCH}_3$ ;
- d) fluorine;
- e) chlorine;
- f)  $\text{-O-G}$ ;
- g)  $\text{-O-G}^1$ ;
- h)  $\text{-O-G}^2$ ;
- i)  $\text{-SO}_3\text{H}$ ; and
- j)  $\text{-PO}_3\text{H}$ ;

provided that when  $R^1$  is H,  $R^{26}$  is not H,  $\text{-OH}$ ,  $\text{-OCH}_3$  or  $\text{-O-G}$ ;

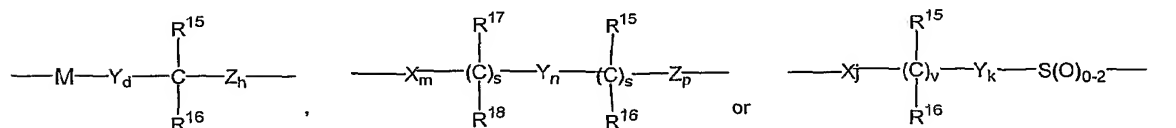
$\text{Ar}^1$  is aryl,  $R^{10}$ -substituted aryl, heteroaryl or  $R^{10}$ -substituted heteroaryl;

$\text{Ar}^2$  is aryl,  $R^{11}$ -substituted aryl, heteroaryl or  $R^{11}$ -substituted heteroaryl;

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L is selected from the group consisting of:

- a) a covalent bond;
- b)  $-(CH_2)_q-$ , wherein q is 1-6;
- c)  $-(CH_2)_e-E-(CH_2)_r-$ , wherein E is  $-O-$ ,  $-C(O)-$ , phenylene,  $-NR^{22}-$  or  $-S(O)_{0-2}-$ , e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;
- d)  $-(C_2-C_6)alkenylene-$ ;
- e)  $-(CH_2)_f-V-(CH_2)_g-$ , wherein V is  $C_3-C_6$ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; and
- f)



wherein M is  $-O-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

X, Y and Z are each independently selected from the group consisting of  $-CH_2-$ ,  $-CH(C_1-C_6)alkyl-$  and  $-C(di-(C_1-C_6)alkyl)-$ ;

$R^8$  is selected from the group consisting of H and alkyl;

$R^{10}$  and  $R^{11}$  are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of  $(C_1-C_6)alkyl$ ,  $-OR^{19}$ ,  $-O(CO)R^{19}$ ,  $-O(CO)OR^{21}$ ,  $-O(CH_2)_{1-5}OR^{19}$ ,  $-O(CO)NR^{19}R^{20}$ ,  $-NR^{19}R^{20}$ ,  $-NR^{19}(CO)R^{20}$ ,  $-NR^{19}(CO)OR^{21}$ ,  $-NR^{19}(CO)NR^{20}R^{25}$ ,  $-NR^{19}SO_2R^{21}$ ,  $-COOR^{19}$ ,  $-CONR^{19}R^{20}$ ,  $-COR^{19}$ ,  $-SO_2NR^{19}R^{20}$ ,  $S(O)_{0-2}R^{21}$ ,  $-O(CH_2)_{1-10}COOR^{19}$ ,  $-O(CH_2)_{1-10}CONR^{19}R^{20}$ ,  $-(C_1-C_6 alkylene)-COOR^{19}$ ,  $-CH=CH-COOR^{19}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$  and halo;

$R^{15}$  and  $R^{17}$  are each independently selected from the group consisting of  $-OR^{19}$ ,  $-OC(O)R^{19}$ ,  $-OC(O)OR^{21}$ ,  $-OC(O)NR^{19}R^{20}$ ;

$R^{16}$  and  $R^{18}$  are each independently selected from the group consisting of H,  $(C_1-C_6)alkyl$  and aryl;

or  $R^{15}$  and  $R^{16}$  together are  $=O$ , or  $R^{17}$  and  $R^{18}$  together are  $=O$ ;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

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s is 0 or 1;

t is 0 or 1;

m, n and p are each independently selected from 0-4;

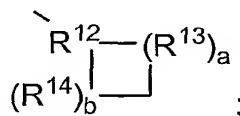
provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

5 provided that when p is 0 and t is 1, the sum of m, n and p is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

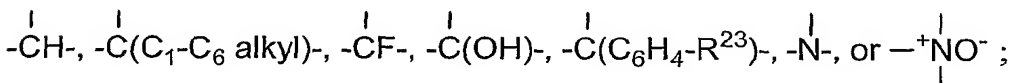
v is 0 or 1;

j and k are each independently 1-5, provided that the sum of j, k and v is 1-5;

10 Q is a bond,  $-(CH_2)_q-$ , wherein q is 1-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group



wherein  $R^{12}$  is



15  $R^{13}$  and  $R^{14}$  are each independently selected from the group consisting of  $-CH_2-$ ,  $-CH(C_1-C_6 \text{ alkyl})-$ ,  $-C(\text{di}-(C_1-C_6) \text{ alkyl})-$ ,  $-CH=CH-$  and  $-C(C_1-C_6 \text{ alkyl})=CH-$ ; or  $R^{12}$  together with an adjacent  $R^{13}$ , or  $R^{12}$  together with an adjacent  $R^{14}$ , form a  $-CH=CH-$  or a  $-CH=C(C_1-C_6 \text{ alkyl})-$  group;

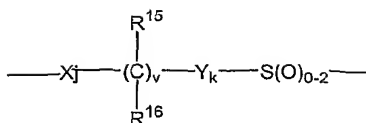
a and b are each independently 0, 1, 2 or 3, provided both are not zero;

20 provided that when  $R^{13}$  is  $-CH=CH-$  or  $-C(C_1-C_6 \text{ alkyl})=CH-$ , a is 1; provided that when  $R^{14}$  is  $-CH=CH-$  or  $-C(C_1-C_6 \text{ alkyl})=CH-$ , b is 1; provided that when a is 2 or 3, the  $R^{13}$ 's can be the same or different; and provided that when b is 2 or 3, the  $R^{14}$ 's can be the same or different;

25 and when Q is a bond and L is



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then Ar<sup>1</sup> can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R<sup>19</sup> and R<sup>20</sup> are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and aryl-substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>21</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl or R<sup>24</sup>-substituted aryl;

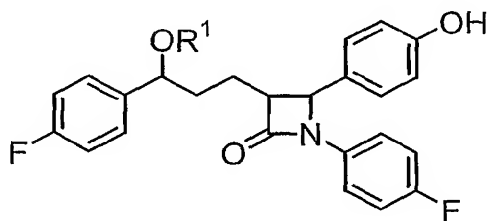
R<sup>22</sup> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)R<sup>19</sup> or -COOR<sup>19</sup>;

R<sup>23</sup> and R<sup>24</sup> are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, -COOH, NO<sub>2</sub>, -NR<sup>19</sup>R<sup>20</sup>, -OH and halo; and

R<sup>25</sup> is H, -OH or (C<sub>1</sub>-C<sub>6</sub>)alkoxy.

Examples of compounds of Formula (IX) which are useful in the methods and combinations of the present invention and methods for making such compounds are disclosed in U.S. Patent Application Serial No. 10/166,942, filed June 11, 2002, incorporated herein by reference.

An example of a useful compound of this invention is one represented by the formula X:

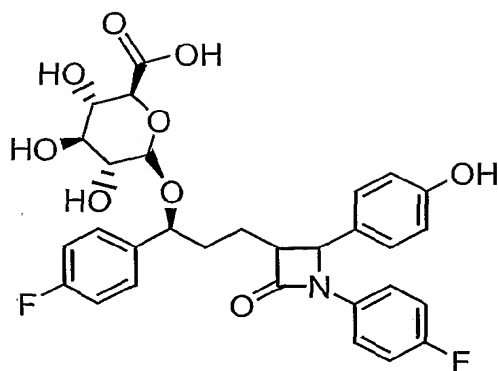


X

wherein R<sup>1</sup> is defined as above.

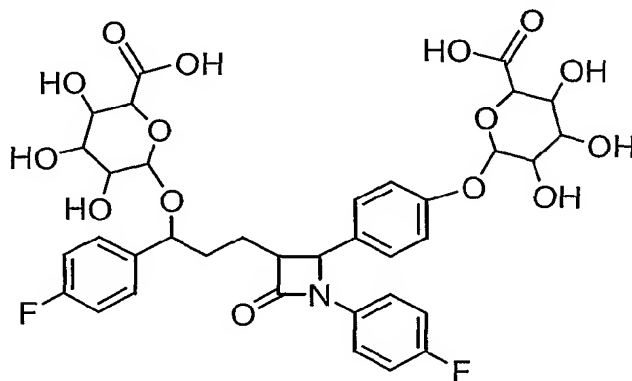
A more preferred compound is one represented by formula XI:

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(XI).

Another useful compound is represented by Formula XII:



XII

Other useful substituted azetidinone compounds include N-sulfonyl-2-azetidinones such as are disclosed in U.S. Patent No. 4,983,597, ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates such as are disclosed in Ram et al., Indian J. Chem. Sect. B. 29B, 12 (1990), p. 1134-7, and diphenyl azetidinones and derivatives disclosed in U.S. Patent Publication Nos. 2002/0039774, 2002/0128252, 2002/0128253 and 2002/0137689, and WO 2002/066464, each of which is incorporated by reference herein.

The compounds of Formulae I-XII can be prepared by known methods, including the methods discussed above and, for example, WO 93/02048 describes the preparation of compounds wherein -R<sup>1</sup>-Q- is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 describes the preparation of compounds wherein Q is a spirocyclic group; WO 95/08532 describes the preparation of compounds wherein -R<sup>1</sup>-Q- is a hydroxy-substituted alkylene group; PCT/US95/03196 describes compounds wherein -R<sup>1</sup>-Q- is a hydroxy-substituted alkylene attached to the Ar<sup>1</sup> moiety through an -O- or S(O)<sub>0-2</sub>-

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group; and U.S. Serial No. 08/463,619, filed June 5, 1995, describes the preparation of compounds wherein -R<sup>1</sup>-Q- is a hydroxy-substituted alkylene group attached the azetidinone ring by a -S(O)<sub>0-2</sub>- group.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, stereoisomers, rotamers, tautomers and racemates of the compounds of Formulae I-XII are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of the Formulae I-XII. Isomers may also include geometric isomers, e.g., when a double bond is present.

Those skilled in the art will appreciate that for some of the compounds of the Formulas I-XII, one isomer will show greater pharmacological activity than other isomers.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

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As used herein, "solvate" means a molecular or ionic complex of molecules or ions of solvent with those of solute (for example, one or more compounds of Formulae I-XII, isomers of the compounds of Formulae I-XII, or prodrugs of the compounds of Formulae I-XII). Non-limiting examples of useful solvents include polar, protic solvents such as water and/or alcohols (for example methanol).

Prodrugs of the compounds of Formulae I-XII are contemplated as being part of this invention. As used herein, "prodrug" means compounds that are drug precursors which, following administration to a patient, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

The daily dose of the sterol absorption inhibitor(s) administered to the subject can range from about 0.1 to about 1000 mg per day, preferably about 0.25 to about 50 mg/day, and more preferably about 10 mg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

For administration of pharmaceutically acceptable salts of the above compounds, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

The term "therapeutically effective amount" means that amount of a therapeutic agent of the composition, such as a sterol absorption inhibitor(s), or other agent useful for the treatment of an autoimmune disorder and other pharmacological or therapeutic agents described below, that will elicit a biological or medical response of a tissue, system, or subject that is being sought by the administrator (such as a researcher, doctor or veterinarian) which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progression of the condition (autoimmune disorder and its symptom(s)).

For example, a widely accepted composite index of improvement in rheumatoid arthritis (RA) is the ACR20 score proposed by the American College of Rheumatology (ACR). ACR20 refers to a composite improvement of 20% in swollen joint count, tender joint count, and 3 or more of the following measures: patient's own global assessment of RA disease activity; physician's assessment of disease

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activity; patient's own assessment of pain due to RA; acute-phase reactant (ESR, CRP); and disability (Health Assessment Questionnaire). See "Guidelines for the Management of Rheumatoid Arthritis, 2002 Update", Arthritis and Rheumatism 46(2): 328-346 (2002). The percentage of patients showing improvement in ACR20 score is the generally accepted minimum criteria for all new therapeutics for the treatment of RA.

Examples of suitable subjects that can be treated according to the methods of the present invention include mammals, such as humans or dogs, and other animals.

As used herein, "combination therapy" or "therapeutic combination" means the administration of two or more therapeutic agents, such as sterol absorption inhibitor(s) and other agents useful for the treatment of an autoimmune disorder, to prevent or treat an autoimmune disorder or any of its associated conditions. Such administration includes coadministration of these therapeutic agents in a substantially simultaneous manner, such as in a single tablet or capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each therapeutic agent. Also, such administration includes use of each type of therapeutic agent in a sequential manner. In either case, the treatment using the combination therapy will provide beneficial effects in treating the autoimmune condition. A potential advantage of the combination therapy disclosed herein may be a reduction in the required amount of an individual therapeutic compound or the overall total amount of therapeutic compounds that are effective in treating the autoimmune condition. By using a combination of therapeutic agents, the side effects of the individual compounds can be reduced as compared to a monotherapy, which can improve patient compliance. Also, therapeutic agents can be selected to provide a broader range of complimentary effects or complimentary modes of action.

In another embodiment, the present invention provides a therapeutic combination comprising (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt thereof or a solvate thereof; and (b) a second amount of at least one other agent or treatment useful for the treatment of an autoimmune disorder, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of an

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autoimmune disorder or lessening or amelioration of one or more symptoms of a condition associated with the autoimmune disorder.

In another embodiment, the present invention provides a pharmaceutical composition for the treatment or prevention of an autoimmune disorder and/or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of a composition comprising (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt thereof or a solvate thereof; (b) a second amount of at least one other agent useful for the treatment of an autoimmune disorder and (c) a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides a method of treating or preventing an autoimmune disorder in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of a composition comprising (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt thereof or a solvate thereof; and (b) a second amount of at least one other agent useful for the treatment of an autoimmune disorder to prevent or treat an autoimmune disorder or any of its symptoms in the subject.

Useful agents for treating autoimmune disorders include: (a) disease modifying antirheumatic drugs, including methotrexate, gold salts, D-penicillamine, hydroxychloroquine, auranofin, sulfasalazine; (b) nonsteroidal antiinflammatory drugs, including indomethacin, naproxen, diclofenac, ibuprofen, aspirin and aspirin analogs, acetaminophen; (c) COX-2 selective inhibitors, including celecoxib, rofecoxib, etoricoxib, valdecoxib, lumiracoxib; (d) COX-1 inhibitors; (e) immunosuppressives, including calcineurin inhibitors such as cyclosporin and FK506; p70<sup>S6</sup> kinase inhibitors such as sirolimus and rapamycin; inosine monophosphate dehydrogenase inhibitors such as mycophenolate; leflunomide, cyclophosphamide, azathioprine; (f) steroids, including prednisone, betamethasone, budesonide and dexamethasone; (g) biological response modifiers, including TNF $\alpha$  antagonists such as infliximab, adalimumab and etanercept; IL-1 receptor antagonists such as anakinra; humanized or chimeric antibodies or fusion proteins such as alefacept, efalizumab, daclizumab; anti-chemokine antibodies or interleukins; and (h) other agents useful for the treatment of autoimmune disorders, including chemokine

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receptor antagonists or modulators, cannabinoid receptor antagonists or modulators, inhibitors of matrix metalloproteinases, TNF $\alpha$ -converting enzymes, nitric oxide synthetases or phosphodiesterase IV, such as roflumilast or cilomilast; inhibitors of p38 MAP-kinase, the NF-kappa $\beta$  pathway or IL-1 receptor associated kinase or  
5 inhibitors of interactions involving adhesion molecules such as LFA-1, VLA-4, ICAM-1, VCAM-1,  $\alpha_4\beta_7$ , MAdCAM-1, and  $\alpha_v\beta_3$ . The amount of the respective agent for treating an autoimmune disorder, which is to administered to the subject can be readily determined by one skilled in the art.

Also useful with the present invention are compositions or therapeutic  
10 combinations that can further comprise one or more pharmacological or therapeutic agents or drugs such as cholesterol biosynthesis inhibitors and/or lipid-lowering agents discussed below.

Non-limiting examples of cholesterol biosynthesis inhibitors for use in the compositions, therapeutic combinations and methods of the present invention  
15 include competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis, squalene synthase inhibitors, squalene epoxidase inhibitors and mixtures thereof. Non-limiting examples of suitable HMG CoA reductase inhibitors include statins such as atorvastatin (for example LIPITOR® which is available from Pfizer), lovastatin (for example MEVACOR® which is available from  
20 Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), fluvastatin, simvastatin (for example ZOCOR® which is available from Merck & Co.), cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate) and pitavastatin (such as NK-104 of Negma Kowa of Japan). Preferred  
25 HMG CoA reductase inhibitors include atorvastatin and simvastatin. Generally, a total daily dosage of cholesterol biosynthesis inhibitor(s) can range from about 0.1 to about 160 mg per day, and preferably about 0.2 to about 80 mg/day in single or 2-3 divided doses.

Also useful with the present invention are compositions or therapeutic  
30 combinations that can further comprise at least one (one or more) activators for peroxisome proliferator-activated receptors (PPAR), such as peroxisome proliferator-

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activated receptor alpha (PPAR $\alpha$ ), peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and peroxisome proliferator-activated receptor delta (PPAR $\delta$ ). PPAR $\alpha$  activator compounds are useful for, among other things, lowering triglycerides, moderately lowering LDL levels and increasing HDL levels. Useful examples of PPAR $\alpha$  activators include fibrates, such as clofibrate, gemfibrozil and fenofibrate. The PPAR activator(s) are administered in a therapeutically effective amount to treat the specified condition, for example in a daily dose preferably ranging from about 50 to about 3000 mg per day.

The compositions, therapeutic combinations or methods of the present invention can further comprise one or more bile acid sequestrants such as cholestyramine, colestipol and colesevelam hydrochloride. Generally, a total daily dosage of bile acid sequestrant(s) can range from about 1 to about 50 grams per day, and preferably about 2 to about 16 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise one or more ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above. The IBAT inhibitors can inhibit bile acid transport to reduce LDL cholesterol levels. Non-limiting examples of suitable IBAT inhibitors include benzothiepinines such as are disclosed in PCT Patent Application WO 00/38727. Generally, a total daily dosage of IBAT inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.1 to about 50 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise nicotinic acid (niacin) and/or derivatives thereof, such as NIASPAN® (niacin extended-release tablets) which are available from Kos. Generally, a total daily dosage of nicotinic acid or a derivative thereof can range from about 500 to about 10,000 mg/day, preferably about 1000 to about 8000 mg/day, and more preferably about 3000 to about 6000 mg/day in single or divided doses.

The compositions or treatments of the present invention can further comprise one or more AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors, which can



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reduce LDL and VLDL levels. Non-limiting examples of useful ACAT inhibitors include avasimibe. Generally, a total daily dosage of ACAT inhibitor(s) can range from about 0.1 to about 1000 mg/day in single or 2-4 divided doses.

5 The compositions or treatments of the present invention can further comprise one or more Cholesteryl Ester Transfer Protein ("CETP") Inhibitors. CETP is responsible for the exchange or transfer of cholesteryl ester carrying HDL and triglycerides in VLDL. Non-limiting examples of suitable CETP inhibitors are disclosed in PCT Patent Application No. WO 00/38721 and U.S. Patent No. 6,147,090, which are incorporated herein by reference. Generally, a total daily  
10 dosage of CETP inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.5 to about 20 mg/kg body weight/day in single or divided doses.

The compositions or treatments of the present invention can further comprise probucol or derivatives thereof, which can reduce LDL levels. Generally, a total daily dosage of probucol or derivatives thereof can range from about 10 to about 2000  
15 mg/day, and preferably about 500 to about 1500 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity. Generally, a total  
20 daily dosage of LDL receptor activator(s) can range from about 1 to about 1000 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise fish oil, which contains Omega 3 fatty acids (3-PUFA), which can reduce VLDL and triglyceride levels. Generally, a total daily dosage of fish oil or Omega 3 fatty acids  
25 can range from about 1 to about 30 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise natural water soluble fibers, such as psyllium, guar, oat and pectin, which can reduce cholesterol levels. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 2-4 divided doses.

30 The compositions or treatments of the present invention can further comprise plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels.

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Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant stanols can range from about 0.5 to about 20 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise  
5 antioxidants, such as probucol, tocopherol, ascorbic acid,  $\beta$ -carotene and selenium, or vitamins such as vitamin B<sub>6</sub> or vitamin B<sub>12</sub>. Generally, a total daily dosage of antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise  
10 monocyte and macrophage inhibitors such as polyunsaturated fatty acids, gene therapy and use of recombinant proteins such as recombinant apo E. Generally, a total daily dosage of these agents can range from about 0.01 to about 1000 mg/day in single or 2-4 divided doses.

The compositions, therapeutic combinations or methods of the present  
15 invention can further comprise one or more cardiovascular agents or blood modifiers.

Mixtures of any of the pharmacological or therapeutic agents described above can be used in the compositions and therapeutic combinations of these other embodiments of the present invention.

The compositions and therapeutic combinations of the present invention can  
20 be administered to a subject in need of such treatment in a therapeutically effective amount to treat an autoimmune disorder and its associated conditions as discussed above. The compositions and treatments can be administered by any suitable means which produce contact of these compounds with the site of action in the body, for example in the plasma, liver or small intestine of a subject.

The daily dosage for the various compositions and therapeutic combinations  
25 described above can be administered to a subject in a single dose or in multiple subdoses, as desired. Subdoses can be administered 2 to 6 times per day, for example. Sustained release dosages can be used. Where the sterol absorption inhibitor(s) and the other agent useful for the treatment of an autoimmune disorder  
30 are administered in separate dosages, the number of doses of each component given per day may not necessarily be the same, e.g., one component may have a greater duration of activity and will therefore need to be administered less frequently.

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The compositions, therapeutic combinations or medicaments of the present invention can further comprise one or more pharmaceutically acceptable carriers, one or more excipients and/or one or more additives. The pharmaceutical compositions can comprise about 1 to about 99 weight percent of active ingredient (such as one or more compounds of Formula I-XII), and preferably about 5 to about 95 percent active ingredient.

Useful pharmaceutically acceptable carriers can be either solid, liquid or gas. Non-limiting examples of pharmaceutically acceptable carriers include solids and/or liquids such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, ethanol, glycerol, water and the like. The amount of carrier in the treatment composition or therapeutic combination can range from about 5 to about 99 weight percent of the total weight of the treatment composition or therapeutic combination. Non-limiting examples of suitable pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders such as starch, polyvinyl pyrrolidone or cellulose ethers, disintegrants such as sodium starch glycolate, crosslinked polyvinyl pyrrolidone or croscarmellose sodium, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, wetting agents such as sodium lauryl sulfate, emulsifiers and the like. The amount of excipient or additive can range from about 0.1 to about 95 weight percent of the total weight of the treatment composition or therapeutic combination. One skilled in the art would understand that the amount of carrier(s), excipients and additives (if present) can vary. Further examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions can be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20<sup>th</sup> Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Useful solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. An example of a preparation of a preferred solid form dosage formulation is provided below.

Useful liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions,

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suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also useful are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

In another embodiment, the present invention provides the use of at least one compound represented by Formulae (I-XII) for manufacture of a medicament (such as one of the compositions discussed above) for the treatment of an autoimmune disorder and its associated conditions.

The following formulation exemplifies one of the dosage forms of this invention. In the formulation, the term "Active Compound I" designates a sterol absorption inhibitor such as any of the compounds of Formulas I-XII described herein above and the term "Active Compound II" designates at least one other agent useful for the treatment of an autoimmune disorder (such as an immunosuppressive medicament) described herein above.

#### EXAMPLE FORMULATION

##### Tablets

<u>No.</u>	<u>Ingredient</u>	<u>mg/tablet</u>
1	Active Compound I	10
2	Lactose monohydrate NF	55
3	Microcrystalline cellulose NF	20

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4	Povidone USP (K29-32)	4
5	Croscarmellose sodium NF	8
6	Sodium lauryl sulfate NF	2
7	Magnesium stearate NF	1
	Total	100

In the present invention, the above-described tablet can be coadministered with an injection, tablet, capsule, etc. comprising a dosage of Active Compound II as described above.

5

#### Method of Manufacture

Mix Item No. 4 with purified water in suitable mixer to form binder solution. Spray the binder solution and then water over Items 1, 2 and 6 and a portion of item 5 in a fluidized bed processor to granulate the ingredients. Continue fluidization to dry the damp granules. Screen the dried granule and blend with Item No. 3 and the remainder of Item No. 5. Add Item No. 7 and mix. Compress the mixture to appropriate size and weight on a suitable tablet machine.

For coadministration in separate tablets or capsules, representative formulations comprising a sterol absorption inhibitor, such as are discussed above, are well known in the art and representative formulations comprising at least one other agent useful for the treatment of an autoimmune disorder, such as are discussed above, are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for sterol absorption inhibitors may readily be modified using the knowledge of one skilled in the art.

Since the present invention relates to treating an autoimmune disorder by treatment with a combination of active ingredients wherein the active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a pharmaceutical composition comprising at least one anti-autoimmune disorder medication and a separate pharmaceutical composition comprising at least one sterol absorption inhibitor as described above. The kit will

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preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g., oral and parenteral) or are administered at different dosage intervals.

5           The treatment compositions and therapeutic combinations of the present invention can inhibit the intestinal absorption of sterols in subjects and can be useful in the treatment and/or prevention of an autoimmune disorder and associated conditions, such as rheumatoid arthritis, in subjects, in particular in mammals.

10           The compositions and therapeutic combinations of the present invention can reduce plasma concentration of at least one sterol selected from the group consisting of cholesterol and phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol) and mixtures thereof. The plasma concentration can be reduced by administering to a subject in need of such treatment an effective amount of at least one treatment composition comprising at least one sterol  
15           absorption inhibitor described above. The reduction in plasma concentration of sterols or can range from about 1 to about 70 percent, and preferably about 10 to about 50 percent. Methods of measuring serum total blood cholesterol and total LDL cholesterol are well known to those skilled in the art and for example include those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein.  
20           Methods of determining levels of other sterols in serum are disclosed in H. Gylling et al., "Serum Sterols During Stanol Ester Feeding in a Mildly Hypercholesterolemic Population", J. Lipid Res. 40: 593-600 (1999), incorporated by reference herein.

25           Illustrating the invention are the following examples which, however, are not to be considered as limiting the invention to their details. Unless otherwise indicated, all parts and percentages in the following examples, as well as throughout the specification, are by weight.

### **EXAMPLES**

30           EXAMPLE 1 - PREPARATION OF COMPOUND OF FORMULA (II)

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Step 1): To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in  $\text{CH}_2\text{Cl}_2$  (200 ml), was added 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethylamine (84.7 ml, 0.61 mol) and the reaction mixture was cooled to  $0^\circ\text{C}$ . Methyl-4-(chloroformyl)butyrate (50 g, 0.3 mol) was added as a solution in  $\text{CH}_2\text{Cl}_2$  (375 ml) dropwise over 1 h, and the reaction was allowed to warm to  $22^\circ\text{C}$ . After 17 h, water and  $\text{H}_2\text{SO}_4$  (2N, 100 ml), was added the layers were separated, and the organic layer was washed sequentially with NaOH (10%), NaCl (sat'd) and water. The organic layer was dried over  $\text{MgSO}_4$  and concentrated to obtain a semicrystalline product.

Step 2): To a solution of  $\text{TiCl}_4$  (18.2 ml, 0.165 mol) in  $\text{CH}_2\text{Cl}_2$  (600 ml) at  $0^\circ\text{C}$ , was added titanium isopropoxide (16.5 ml, 0.055 mol). After 15 min, the product of Step 1 (49.0 g, 0.17 mol) was added as a solution in  $\text{CH}_2\text{Cl}_2$  (100 ml). After 5 min., diisopropylethylamine (DIPEA) (65.2 ml, 0.37 mol) was added and the reaction mixture was stirred at  $0^\circ\text{C}$  for 1 h, the reaction mixture was cooled to  $-20^\circ\text{C}$ , and 4-benzyloxybenzylidene(4-fluoro)aniline (114.3 g, 0.37 mol) was added as a solid. The reaction mixture was stirred vigorously for 4 h at  $-20^\circ\text{C}$ , then acetic acid was added as a solution in  $\text{CH}_2\text{Cl}_2$  dropwise over 15 min, the reaction mixture was allowed to warm to  $0^\circ\text{C}$ , and  $\text{H}_2\text{SO}_4$  (2N) was added. The reaction mixture was stirred an additional 1 h, the layers were separated, washed with water, separated and the organic layer was dried. The crude product was crystallized from ethanol/water to obtain the pure intermediate.

Step 3): To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene (100 ml) at  $50^\circ\text{C}$ , was added N,O-bis(trimethylsilyl)acetamide (BSA) (7.50 ml, 30.3 mmol). After 0.5 h, solid TBAF (0.39 g, 1.5 mmol) was added and the reaction mixture stirred at  $50^\circ\text{C}$  for an additional 3 h. The reaction mixture was cooled to  $22^\circ\text{C}$ ,  $\text{CH}_3\text{OH}$  (10 ml), was added. The reaction mixture was washed with HCl (1N),  $\text{NaHCO}_3$  (1N) and NaCl (sat'd.), and the organic layer was dried over  $\text{MgSO}_4$ .

Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) in  $\text{CH}_3\text{OH}$  (3 ml), was added water (1 ml) and  $\text{LiOH}\cdot\text{H}_2\text{O}$  (102 mg, 2.4 mmole). The reaction

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mixture was stirred at 22°C for 1 h and then additional LiOH·H<sub>2</sub>O (54 mg, 1.3 mmole) was added. After a total of 2 h, HCl (1N) and EtOAc was added, the layers were separated, the organic layer was dried and concentrated in *vacuo*. To a solution of the resultant product (0.91 g, 2.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 22°C, was added  
5 ClCOCOCI (0.29 ml, 3.3 mmol) and the mixture stirred for 16 h. The solvent was removed in *vacuo*.

Step 5): To an efficiently stirred suspension of 4-fluorophenylzinc chloride (4.4 mmol) prepared from 4-fluorophenylmagnesium bromide (1M in THF, 4.4 ml, 4.4 mmol) and ZnCl<sub>2</sub> (0.6 g, 4.4 mmol) at 4°C, was added tetrakis(triphenyl-  
10 phosphine)palladium (0.25 g, 0.21 mmol) followed by the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 ml). The reaction was stirred for 1 h at 0°C and then for 0.5 h at 22°C. HCl (1N, 5 ml) was added and the mixture was extracted with EtOAc. The organic layer was concentrated to an oil and purified by silica gel chromatography to obtain 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(3-oxo-3-  
15 phenylpropyl)-2-azetidinone:

HRMS calc'd for C<sub>24</sub>H<sub>19</sub>F<sub>2</sub>NO<sub>3</sub> = 408.1429, found 408.1411.

Step 6): To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 ml), was added (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole (120 mg, 0.43 mmol) and the mixture was cooled to -20°C. After 5 min,  
20 borohydride-dimethylsulfide complex (2M in THF, 0.85 ml, 1.7 mmol) was added dropwise over 0.5 h. After a total of 1.5 h, CH<sub>3</sub>OH was added followed by HCl (1 N) and the reaction mixture was extracted with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. <sup>1</sup>H in CDCl<sub>3</sub> d H<sub>3</sub> = 4.68. J = 2.3 Hz. Cl  
25 (M<sup>+</sup>H) 500.

Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). <sup>1</sup>H in CDCl<sub>3</sub> d H<sub>3</sub> = 4.69. J = 2.3 Hz. Cl (M<sup>+</sup>H) 500.

To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 ml), was  
30 added 10% Pd/C (0.03 g) and the reaction mixture was stirred under a pressure (60



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psi) of H<sub>2</sub> gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to obtain compound 6A. Mp 164-166°C; CI (M<sup>+</sup>H) 410.

$[\alpha]_D^{25} = -28.1^\circ$  (c 3, CH<sub>3</sub>OH). Elemental analysis calc'd for C<sub>24</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>3</sub>: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

5 Similarly treat compound 6B-1 to obtain compound 6B.

Mp 129.5-132.5°C; CI (M<sup>+</sup>H) 410. Elemental analysis calc'd for C<sub>24</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>3</sub>: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

10 Step 6' (Alternative): To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 ml), was added 10% Pd/C (0.03 g) and the reaction was stirred under a pressure (60 psi) of H<sub>2</sub> gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to afford a 1:1 mixture of compounds 6A and 6B.

#### EXAMPLE 2 - HYPOTHETICAL *IN VIVO* EVALUATION OF THE ABILITY OF THE COMPOUND OF FORMULA II TO TREAT EXPERIMENTAL ARTHRITIS

15 The compound of Formula II (or any cholesterol absorption inhibitor discussed above) is administered to rodents which have been induced to develop experimental arthritis. Useful rodents can include Balb/c, C57BL/6, B10.RIII or DBA/1 mice, or Lewis or Wistar rats (available from Jackson Laboratory, Charles River Laboratories or Taconic Laboratories).

20 In the present example, collagen-induced arthritis (CIA) in DBA/1 or B10.RIII mice (from the Jackson Laboratory) are used as an animal model of rheumatoid arthritis for *in vivo* evaluation of the effect of the compound of Formula II on rheumatoid disease. Typically, the highly susceptible parental strain DBA/1 or  
25 B10.RIII develop 90-100% arthritis in males and 60-100% arthritis in females. The disease is induced by immunization with cartilage-specific type II collagen in Complete Freund's adjuvant and in some cases animals are boosted with Type II collagen or lipopolysaccharide on days 17-25 after immunization. The mice are 8-10 weeks old at the time of immunization. Rat type II collagen is prepared as previously  
30 described (see Miller and Rhodes (1982) Methods Enzymol. 82: 33). CIA is induced by intradermal immunization in the base of the tail with 50-100 µg type II collagen

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emulsified in Complete Freund's adjuvant (as described in Current Protocols in Immunology, Unit 15, John Wiley & Sons, Inc. NY or in Holmdahl, et al. (1998) Genetic Analysis of Murine Models for Rheumatoid Arthritis *In Human Genome Methods*, vol. 215, CRC Press, NY).

5           The compound of Formula II (or any cholesterol absorption inhibitor discussed above) is administered to mice that have been induced to developed CIA. Typically, mice can be scored for clinical disease starting at 14 days after immunization with rat type II collagen. The compound of Formula II is administered at a dosage of 0.1-100 mg/kg/day either in the diet or by systemic oral, subcutaneous or intraperitoneal  
10       administration over a period of 3 days to 10 weeks. Animals are scored daily for clinical disease score as described in Current Protocols in Immunology, Unit 15, John Wiley & Sons, Inc., NY. At a specified period of time after compound administration, animals are euthanized by isofurane overdose and cytological, histological, immunological and immunohistochemical parameters are assessed by  
15       standard techniques well known to those skilled in the art. Serum lipoprotein and cholesterol measurements will be made by methods well known to those skilled in the art and, for example, including those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein.

20       EXAMPLE 3 - HYPOTHETICAL IN VIVO EVALUATION OF THE ABILITY OF THE COMPOUND OF FORMULA II TO TREAT ULCERATIVE COLITIS

          The compound of Formula II (or any cholesterol absorption inhibitor discussed above) is administered to rodents which have been induced to develop ulcerative  
25       colitis. Suitable rodents are the same as those described in Example 2.

          In the present example, the effect of the administration of the compound of Formula II is investigated in 2,4,6-trinitrobenzene sulfonic acid (TNBS) - induced colitis in mice. The compound of Formula II is administered at a dosage of 0.1-100 mg/kg/day either in the diet or by systemic oral, subcutaneous or intraperitoneal  
30       administration over a period of 3 days to 10 weeks. Colitis is induced in mice by intrarectal administration of TNBS (1.5 mg/mouse in 50% ethanol) and disease

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severity is assessed clinically and by histologic scoring of colon damage, including determination of interleukin (IL)-2, IL-12, interferon (INF)-gamma and tumor necrosis factor (TNF)-alpha (protein and mRNA) and myeloperoxidase (MPO) activity in the colon. Cytokine production by the lamina propria mononuclear cells (LPMC) and luminal bacteria are also typically measured (see Fiorucci, et al. (2002) Digestion 66(4): 246-256). In particular, after a specified period of time after Compound II administration, animals are euthanized by isofurane overdose and the above-described parameters are assessed using methods described in Current Protocols in Immunology, Unit 15, John Wiley & Sons, Inc. NY and/or using the methods described by Fiorucci, et al. (2002) in Digestion 66(4): 246-256. Serum lipoprotein and cholesterol measurements will be made as described in Example 2.

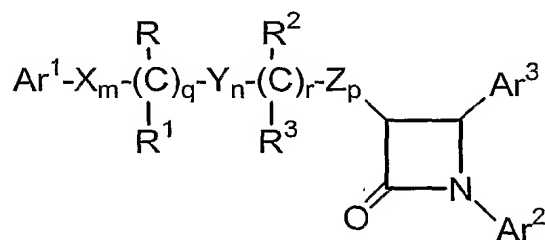
It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

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THEREFORE, WE CLAIM:

1. A method of treating or preventing an autoimmune disorder in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof.

2. The method according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein:

$\text{Ar}^1$  and  $\text{Ar}^2$  are independently selected from the group consisting of aryl and  $\text{R}^4$ -substituted aryl;

$\text{Ar}^3$  is aryl or  $\text{R}^5$ -substituted aryl;

X, Y and Z are independently selected from the group consisting of  $-\text{CH}_2-$ ,  $-\text{CH}(\text{lower alkyl})-$  and  $-\text{C}(\text{dilower alkyl})-$ ;

R and  $\text{R}^2$  are independently selected from the group consisting of  $-\text{OR}^6$ ,  $-\text{O}(\text{CO})\text{R}^6$ ,  $-\text{O}(\text{CO})\text{OR}^9$  and  $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$ ;

$\text{R}^1$  and  $\text{R}^3$  are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

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m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

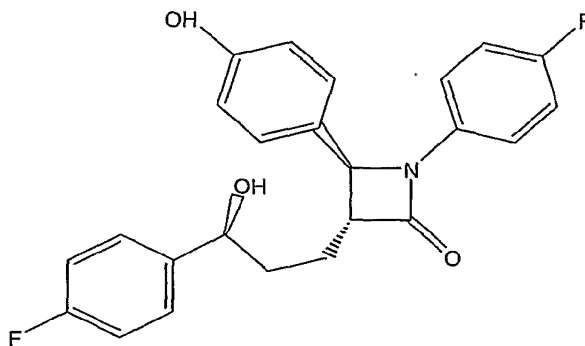
$R^4$  is 1-5 substituents independently selected from the group consisting of lower alkyl,  $-OR^6$ ,  $-O(CO)R^6$ ,  $-O(CO)OR^9$ ,  $-O(CH_2)_{1-5}OR^6$ ,  $-O(CO)NR^6R^7$ ,  $-NR^6R^7$ ,  $-NR^6(CO)R^7$ ,  $-NR^6(CO)OR^9$ ,  $-NR^6(CO)NR^7R^8$ ,  $-NR^6SO_2R^9$ ,  $-COOR^6$ ,  $-CONR^6R^7$ ,  $-COR^6$ ,  $-SO_2NR^6R^7$ ,  $S(O)_{0-2}R^9$ ,  $-O(CH_2)_{1-10}-COOR^6$ ,  $-O(CH_2)_{1-10}CONR^6R^7$ ,  $-(lower\ alkylene)COOR^6$ ,  $-CH=CH-COOR^6$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$  and halogen;

$R^5$  is 1-5 substituents independently selected from the group consisting of  $-OR^6$ ,  $-O(CO)R^6$ ,  $-O(CO)OR^9$ ,  $-O(CH_2)_{1-5}OR^6$ ,  $-O(CO)NR^6R^7$ ,  $-NR^6R^7$ ,  $-NR^6(CO)R^7$ ,  $-NR^6(CO)OR^9$ ,  $-NR^6(CO)NR^7R^8$ ,  $-NR^6SO_2R^9$ ,  $-COOR^6$ ,  $-CONR^6R^7$ ,  $-COR^6$ ,  $-SO_2NR^6R^7$ ,  $S(O)_{0-2}R^9$ ,  $-O(CH_2)_{1-10}-COOR^6$ ,  $-O(CH_2)_{1-10}CONR^6R^7$ ,  $-(lower\ alkylene)COOR^6$  and  $-CH=CH-COOR^6$ ;

$R^6$ ,  $R^7$  and  $R^8$  are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

$R^9$  is lower alkyl, aryl or aryl-substituted lower alkyl.

3. The method according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (II):



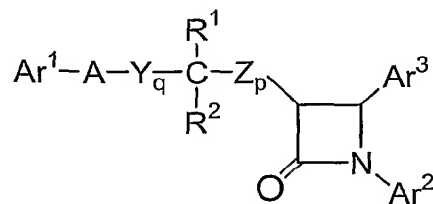
(II)

or a pharmaceutically acceptable salt or solvate thereof.

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4. The method according to claim 1, wherein the at least one sterol absorption inhibitor is selected from the group of compounds represented by:

(a) Formula (III):



(III)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein in Formula (III) above:

Ar<sup>1</sup> is R<sup>3</sup>-substituted aryl;

Ar<sup>2</sup> is R<sup>4</sup>-substituted aryl;

Ar<sup>3</sup> is R<sup>5</sup>-substituted aryl;

Y and Z are independently selected from the group consisting of -CH<sub>2</sub>-, -CH(lower alkyl)- and -C(dilower alkyl)-;

A is selected from -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-;

R<sup>1</sup> is selected from the group consisting of -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup> and -O(CO)NR<sup>6</sup>R<sup>7</sup>; R<sup>2</sup> is selected from the group consisting of hydrogen, lower alkyl and aryl; or R<sup>1</sup> and R<sup>2</sup> together are =O;

q is 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

R<sup>5</sup> is 1-3 substituents independently selected from the group consisting of -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>9</sup>, -O(CO)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(CO)R<sup>7</sup>, -NR<sup>6</sup>(CO)OR<sup>9</sup>, -NR<sup>6</sup>(CO)NR<sup>7</sup>R<sup>8</sup>, -NR<sup>6</sup>SO<sub>2</sub>-lower alkyl, -NR<sup>6</sup>SO<sub>2</sub>-aryl, -CONR<sup>6</sup>R<sup>7</sup>, -COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, S(O)<sub>0-2</sub>-alkyl, S(O)<sub>0-2</sub>-aryl, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>6</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>6</sup>R<sup>7</sup>, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-COOR<sup>6</sup>, and

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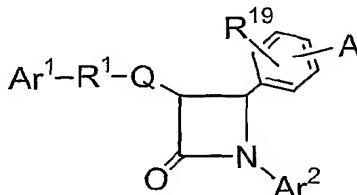
-CH=CH-COOR<sup>6</sup>;

R<sup>3</sup> and R<sup>4</sup> are independently 1-3 substituents independently selected from the group consisting of R<sup>5</sup>, hydrogen, p-lower alkyl, aryl, -NO<sub>2</sub>, -CF<sub>3</sub> and p-halogeno;

R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R<sup>9</sup> is lower alkyl, aryl or aryl-substituted lower alkyl;

(b) Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein in Formula (IV) above:

A is selected from the group consisting of R<sup>2</sup>-substituted heterocycloalkyl, R<sup>2</sup>-substituted heteroaryl, R<sup>2</sup>-substituted benzofused heterocycloalkyl, and R<sup>2</sup>-substituted benzofused heteroaryl;

Ar<sup>1</sup> is aryl or R<sup>3</sup>-substituted aryl;

Ar<sup>2</sup> is aryl or R<sup>4</sup>-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the

spiro group ; and

R<sup>1</sup> is selected from the group consisting of:

-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

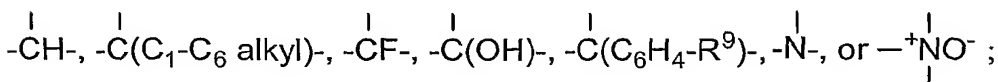
-(CH<sub>2</sub>)<sub>e</sub>-G-(CH<sub>2</sub>)<sub>r</sub>-, wherein G is -O-, -C(O)-, phenylene, -NR<sup>8</sup>- or -S(O)<sub>0-2</sub>-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-; and

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$-(CH_2)_fV-(CH_2)_g-$ , wherein V is  $C_3$ - $C_6$  cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

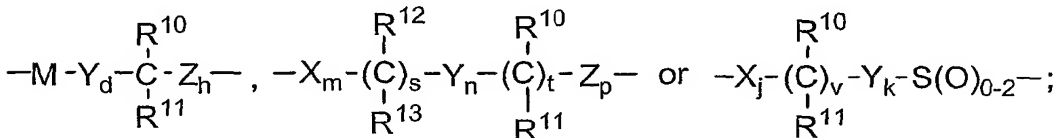
$R^5$  is selected from:



$R^6$  and  $R^7$  are independently selected from the group consisting of  $-CH_2-$ ,  $-CH(C_1-C_6 \text{ alkyl})-$ ,  $-C(\text{di-}(C_1-C_6) \text{ alkyl})-$ ,  $-CH=CH-$  and  $-C(C_1-C_6 \text{ alkyl})=CH-$ ; or  $R^5$  together with an adjacent  $R^6$ , or  $R^5$  together with an adjacent  $R^7$ , form a  $-CH=CH-$  or a  $-CH=C(C_1-C_6 \text{ alkyl})-$  group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when  $R^6$  is  $-CH=CH-$  or  $-C(C_1-C_6 \text{ alkyl})=CH-$ , a is 1; provided that when  $R^7$  is  $-CH=CH-$  or  $-C(C_1-C_6 \text{ alkyl})=CH-$ , b is 1; provided that when a is 2 or 3, the  $R^6$ 's can be the same or different; and provided that when b is 2 or 3, the  $R^7$ 's can be the same or different;

and when Q is a bond,  $R^1$  also can be selected from:



where M is  $-O-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

X, Y and Z are independently selected from the group consisting of  $-CH_2-$ ,  $-CH(C_1-C_6 \text{ alkyl})-$  and  $-C(\text{di-}(C_1-C_6) \text{ alkyl})-$ ;

$R^{10}$  and  $R^{12}$  are independently selected from the group consisting of  $-OR^{14}$ ,  $-O(CO)R^{14}$ ,  $-O(CO)OR^{16}$  and  $-O(CO)NR^{14}R^{15}$ ;

$R^{11}$  and  $R^{13}$  are independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl and aryl; or  $R^{10}$  and  $R^{11}$  together are  $=O$ , or  $R^{12}$  and  $R^{13}$  together are  $=O$ ;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;



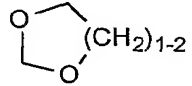
- 56 -

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

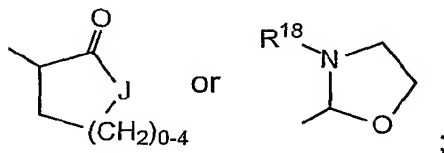
v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

$R^2$  is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen,  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl,  $(C_3-C_6)$ cycloalkyl,  $(C_3-C_6)$ cycloalkenyl,  $R^{17}$ -substituted aryl,  $R^{17}$ -substituted benzyl,  $R^{17}$ -substituted benzyloxy,  $R^{17}$ -substituted aryloxy, halogeno,  $-NR^{14}R^{15}$ ,  $NR^{14}R^{15}(C_1-C_6 \text{ alkylene})-$ ,  $NR^{14}R^{15}C(O)(C_1-C_6 \text{ alkylene})-$ ,  $-NHC(O)R^{16}$ , OH,  $C_1-C_6$  alkoxy,  $-OC(O)R^{16}$ ,  $-COR^{14}$ , hydroxy $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy $(C_1-C_6)$ alkyl,  $NO_2$ ,  $-S(O)_{0-2}R^{16}$ ,  $-SO_2NR^{14}R^{15}$  and  $-(C_1-C_6 \text{ alkylene})COOR^{14}$ ; when  $R^2$  is a

substituent on a heterocycloalkyl ring,  $R^2$  is as defined, or is  $=O$  or  ;

and, where  $R^2$  is a substituent on a substitutable ring nitrogen, it is hydrogen,  $(C_1-C_6)$ alkyl, aryl,  $(C_1-C_6)$ alkoxy, aryloxy,  $(C_1-C_6)$ alkylcarbonyl, arylcarbonyl, hydroxy,  $-(CH_2)_{1-6}CONR^{18}R^{18}$ ,



wherein J is  $-O-$ ,  $-NH-$ ,  $-NR^{18}-$  or  $-CH_2-$ ;

$R^3$  and  $R^4$  are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of  $(C_1-C_6)$ alkyl,  $-OR^{14}$ ,  $-O(CO)R^{14}$ ,  $-O(CO)OR^{16}$ ,  $-O(CH_2)_{1-5}OR^{14}$ ,  $-O(CO)NR^{14}R^{15}$ ,  $-NR^{14}R^{15}$ ,  $-NR^{14}(CO)R^{15}$ ,  $-NR^{14}(CO)OR^{16}$ ,  $-NR^{14}(CO)NR^{15}R^{19}$ ,  $-NR^{14}SO_2R^{16}$ ,  $-COOR^{14}$ ,  $-CONR^{14}R^{15}$ ,  $-COR^{14}$ ,  $-SO_2NR^{14}R^{15}$ ,  $S(O)_{0-2}R^{16}$ ,  $-O(CH_2)_{1-10}-COOR^{14}$ ,

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-O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>14</sup>R<sup>15</sup>, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-COOR<sup>14</sup>, -CH=CH-COOR<sup>14</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub> and halogen;

R<sup>8</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)R<sup>14</sup> or -COOR<sup>14</sup>;

R<sup>9</sup> and R<sup>17</sup> are independently 1-3 groups independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, -COOH, NO<sub>2</sub>, -NR<sup>14</sup>R<sup>15</sup>, OH and halogeno;

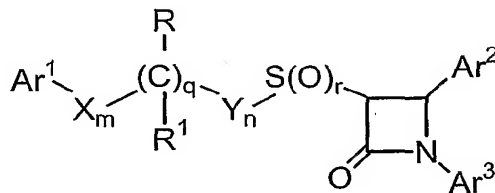
R<sup>14</sup> and R<sup>15</sup> are independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and aryl-substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>16</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl or R<sup>17</sup>-substituted aryl;

R<sup>18</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl; and

R<sup>19</sup> is hydrogen, hydroxy or (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

(c) Formula (V):



(V)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein in Formula (V) above:

Ar<sup>1</sup> is aryl, R<sup>10</sup>-substituted aryl or heteroaryl;

Ar<sup>2</sup> is aryl or R<sup>4</sup>-substituted aryl;

Ar<sup>3</sup> is aryl or R<sup>5</sup>-substituted aryl;

X and Y are independently selected from the group consisting of -CH<sub>2</sub>-, -CH(lower alkyl)- and -C(dilower alkyl)-;

R is -OR<sup>6</sup>, -O(CO)R<sup>6</sup>, -O(CO)OR<sup>9</sup> or -O(CO)NR<sup>6</sup>R<sup>7</sup>; R<sup>1</sup> is hydrogen, lower alkyl or aryl; or R and R<sup>1</sup> together are =O;

q is 0 or 1;

r is 0, 1 or 2;

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m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

$R^4$  is 1-5 substituents independently selected from the group consisting of lower alkyl,  $-OR^6$ ,  $-O(CO)R^6$ ,  $-O(CO)OR^9$ ,  $-O(CH_2)_{1-5}OR^6$ ,  $-O(CO)NR^6R^7$ ,  
 5  $-NR^6R^7$ ,  $-NR^6(CO)R^7$ ,  $-NR^6(CO)OR^9$ ,  $-NR^6(CO)NR^7R^8$ ,  $-NR^6SO_2R^9$ ,  $-COOR^6$ ,  
 $-CONR^6R^7$ ,  $-COR^6$ ,  $-SO_2NR^6R^7$ ,  $S(O)_{0-2}R^9$ ,  $-O(CH_2)_{1-10}-COOR^6$ ,  
 $-O(CH_2)_{1-10}CONR^6R^7$ ,  $-(lower\ alkylene)COOR^6$  and  $-CH=CH-COOR^6$ ;

$R^5$  is 1-5 substituents independently selected from the group consisting of  $-OR^6$ ,  $-O(CO)R^6$ ,  $-O(CO)OR^9$ ,  $-O(CH_2)_{1-5}OR^6$ ,  $-O(CO)NR^6R^7$ ,  $-NR^6R^7$ ,  $-NR^6(CO)R^7$ ,  
 10  $-NR^6(CO)OR^9$ ,  $-NR^6(CO)NR^7R^8$ ,  $-NR^6SO_2R^9$ ,  $-COOR^6$ ,  $-CONR^6R^7$ ,  $-COR^6$ ,  $-SO_2NR^6R^7$ ,  $S(O)_{0-2}R^9$ ,  $-O(CH_2)_{1-10}-COOR^6$ ,  $-O(CH_2)_{1-10}CONR^6R^7$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  
 halogen,  
 $-(lower\ alkylene)COOR^6$  and  $-CH=CH-COOR^6$ ;

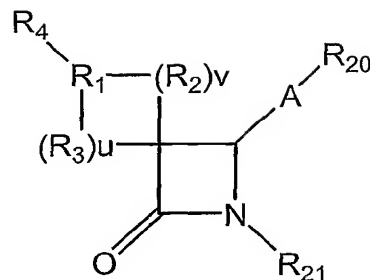
$R^6$ ,  $R^7$  and  $R^8$  are independently selected from the group consisting of  
 15 hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

$R^9$  is lower alkyl, aryl or aryl-substituted lower alkyl; and

$R^{10}$  is 1-5 substituents independently selected from the group consisting of lower alkyl,  $-OR^6$ ,  $-O(CO)R^6$ ,  $-O(CO)OR^9$ ,  $-O(CH_2)_{1-5}OR^6$ ,  $-O(CO)NR^6R^7$ ,  
 20  $-NR^6R^7$ ,  $-NR^6(CO)R^7$ ,  $-NR^6(CO)OR^9$ ,  $-NR^6(CO)NR^7R^8$ ,  $-NR^6SO_2R^9$ ,  $-COOR^6$ ,  
 $-CONR^6R^7$ ,  $-COR^6$ ,  $-SO_2NR^6R^7$ ,  $-S(O)_{0-2}R^9$ ,  $-O(CH_2)_{1-10}-COOR^6$ ,  
 $-O(CH_2)_{1-10}CONR^6R^7$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$  and halogen;

(d) Formula (VI):

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(VI)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein in Formula (VI) above:

R<sub>1</sub> is

-CH-, -C(lower alkyl)-, -CF-, -C(OH)-, -C(C<sub>6</sub>H<sub>5</sub>)-, -C(C<sub>6</sub>H<sub>4</sub>-R<sub>15</sub>)-,  
 -N- or -<sup>+</sup>N O<sup>-</sup> ;

R<sub>2</sub> and R<sub>3</sub> are independently selected from the group consisting of:

-CH<sub>2</sub>-, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower alkyl)=CH-; or

R<sub>1</sub> together with an adjacent R<sub>2</sub>, or R<sub>1</sub> together with an adjacent R<sub>3</sub>, form a  
 -CH=CH- or a -CH=C(lower alkyl)- group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R<sub>2</sub> is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R<sub>3</sub> is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R<sub>2</sub>'s can be the same or different; and provided that when u is 2 or 3, the R<sub>3</sub>'s can be the same or different;

R<sub>4</sub> is selected from B-(CH<sub>2</sub>)<sub>m</sub>C(O)-, wherein m is 0, 1, 2, 3, 4 or 5;

B-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 0, 1, 2, 3, 4, 5 or 6;

B-(CH<sub>2</sub>)<sub>e</sub>-Z-(CH<sub>2</sub>)<sub>r</sub>-, wherein Z is -O-, -C(O)-, phenylene, -N(R<sub>8</sub>)- or -S(O)<sub>0-2</sub>-, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6;

B-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-;

B-(C<sub>4</sub>-C<sub>6</sub> alkadienylene)-;

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B-(CH<sub>2</sub>)<sub>t</sub>-Z-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B-(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

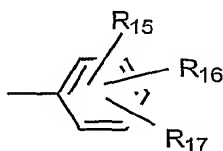
B-(CH<sub>2</sub>)<sub>t</sub>-V-(C<sub>2</sub>-C<sub>6</sub> alkenylene)- or

B-(C<sub>2</sub>-C<sub>6</sub> alkenylene)-V-(CH<sub>2</sub>)<sub>t</sub>-, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B-(CH<sub>2</sub>)<sub>a</sub>-Z-(CH<sub>2</sub>)<sub>b</sub>-V-(CH<sub>2</sub>)<sub>d</sub>-, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6; or T-(CH<sub>2</sub>)<sub>s</sub>-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R<sub>1</sub> and R<sub>4</sub> together form the group  $\text{B}-\text{CH}=\overset{\text{I}}{\text{C}}-$ ;

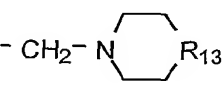
B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, -CF<sub>3</sub>, -OCF<sub>3</sub>, benzyl, R<sub>7</sub>-benzyl, benzyloxy, R<sub>7</sub>-benzyloxy, phenoxy, R<sub>7</sub>-phenoxy, dioxolanyl, NO<sub>2</sub>-, N(R<sub>8</sub>)(R<sub>9</sub>), N(R<sub>8</sub>)(R<sub>9</sub>)-lower alkylene-, N(R<sub>8</sub>)(R<sub>9</sub>)-lower alkyleneoxy-, OH, halogeno-, -CN, -N<sub>3</sub>, -NHC(O)OR<sub>10</sub>,

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-NHC(O)R<sub>10</sub>, R<sub>11</sub>O<sub>2</sub>SNH-, (R<sub>11</sub>O<sub>2</sub>S)<sub>2</sub>N-, -S(O)<sub>2</sub>NH<sub>2</sub>, -S(O)<sub>0-2</sub>R<sub>8</sub>, tert-butyl-dimethyl-silyloxymethyl, -C(O)R<sub>12</sub>, -COOR<sub>19</sub>, -CON(R<sub>8</sub>)(R<sub>9</sub>), -CH=CHC(O)R<sub>12</sub>, -lower alkylene-C(O)R<sub>12</sub>, R<sub>10</sub>C(O)(lower alkyleneoxy)-,

N(R<sub>8</sub>)(R<sub>9</sub>)C(O)(lower alkyleneoxy)- and  for substitution on ring carbon atoms,

and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR<sub>10</sub>, -C(O)R<sub>10</sub>, OH, N(R<sub>8</sub>)(R<sub>9</sub>)-lower alkylene-, N(R<sub>8</sub>)(R<sub>9</sub>)-lower alkyleneoxy-, -S(O)<sub>2</sub>NH<sub>2</sub> and 2-(trimethylsilyl)-ethoxymethyl;

R<sub>7</sub> is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO<sub>2</sub>, -N(R<sub>8</sub>)(R<sub>9</sub>), OH, and halogeno;

R<sub>8</sub> and R<sub>9</sub> are independently selected from H or lower alkyl;

R<sub>10</sub> is selected from lower alkyl, phenyl, R<sub>7</sub>-phenyl, benzyl or R<sub>7</sub>-benzyl;

R<sub>11</sub> is selected from OH, lower alkyl, phenyl, benzyl, R<sub>7</sub>-phenyl or R<sub>7</sub>-benzyl;

R<sub>12</sub> is selected from H, OH, alkoxy, phenoxy, benzyloxy,

, -N(R<sub>8</sub>)(R<sub>9</sub>), lower alkyl, phenyl or R<sub>7</sub>-phenyl;

R<sub>13</sub> is selected from -O-, -CH<sub>2</sub>-, -NH-, -N(lower alkyl)- or -NC(O)R<sub>19</sub>;

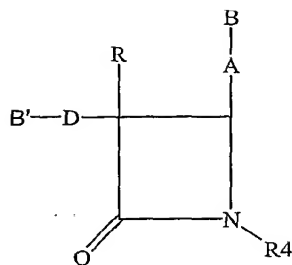
R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub> are independently selected from the group consisting of H and the groups defined for W; or R<sub>15</sub> is hydrogen and R<sub>16</sub> and R<sub>17</sub>, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R<sub>19</sub> is H, lower alkyl, phenyl or phenyl lower alkyl; and

R<sub>20</sub> and R<sub>21</sub> are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above;

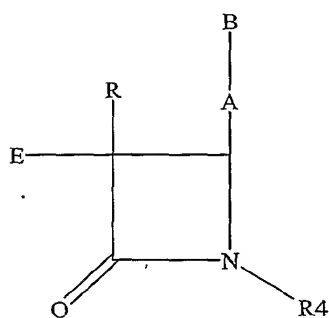
(e) Formula (VIIA) or (VIIB):

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(VIIA)

or



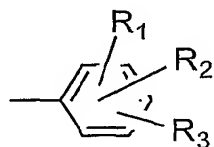
(VIIB)

or a pharmaceutically acceptable salt or solvate thereof,

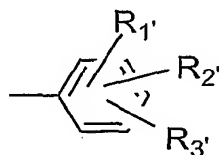
wherein in Formula (VIIA) or (VIIB) above:

A is -CH=CH-, -C≡C- or -(CH<sub>2</sub>)<sub>p</sub>- wherein p is 0, 1 or 2;

B is



B' is



D is -(CH<sub>2</sub>)<sub>m</sub>C(O)- or -(CH<sub>2</sub>)<sub>q</sub>- wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

E is C<sub>10</sub> to C<sub>20</sub> alkyl or -C(O)-(C<sub>9</sub> to C<sub>19</sub>)-alkyl, wherein the alkyl is straight

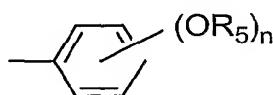
or branched, saturated or containing one or more double bonds;

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R is hydrogen, C<sub>1</sub>-C<sub>15</sub> alkyl, straight or branched, saturated or containing one or more double bonds, or B-(CH<sub>2</sub>)<sub>r</sub>-, wherein r is 0, 1, 2, or 3;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>1'</sub>, R<sub>2'</sub>, and R<sub>3'</sub> are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO<sub>2</sub>, NH<sub>2</sub>, OH, halogeno, lower alkylamino, dilower alkylamino, -NHC(O)OR<sub>5</sub>, R<sub>6</sub>O<sub>2</sub>SNH- and -S(O)<sub>2</sub>NH<sub>2</sub>;

R<sub>4</sub> is



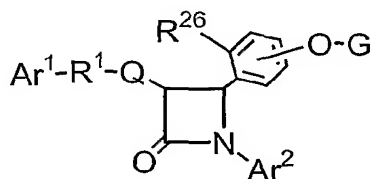
wherein n is 0, 1, 2 or 3;

R<sub>5</sub> is lower alkyl; and

R<sub>6</sub> is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO<sub>2</sub>, NH<sub>2</sub>, OH, halogeno, lower alkylamino and dilower alkylamino;

or a pharmaceutically acceptable salt thereof or a prodrug thereof;

(f) Formula (VIII):

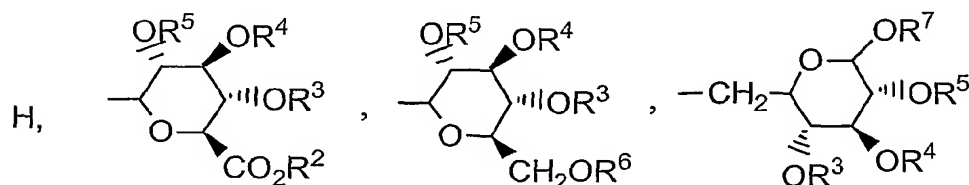


(VIII)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein in Formula (VIII) above,

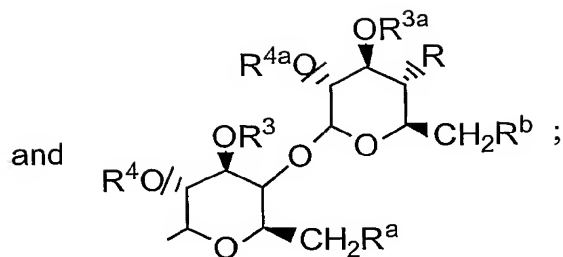
R<sup>26</sup> is H or OG<sup>1</sup>;

G and G<sup>1</sup> are independently selected from the group consisting of





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provided that when R<sup>26</sup> is H or

OH, G is not H;

R, R<sup>a</sup> and R<sup>b</sup> are independently selected from the group consisting of H, -OH, halogeno, -NH<sub>2</sub>, azido, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)-alkoxy or -W-R<sup>30</sup>;

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R<sup>31</sup>)-, -NH-C(O)-N(R<sup>31</sup>)- and -O-C(S)-N(R<sup>31</sup>)-;

R<sup>2</sup> and R<sup>6</sup> are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup>, R<sup>3a</sup> and R<sup>4a</sup> are independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl and -C(O)aryl;

R<sup>30</sup> is selected from the group consisting of R<sup>32</sup>-substituted T, R<sup>32</sup>-substituted-T-(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sup>32</sup>-substituted-(C<sub>2</sub>-C<sub>4</sub>)alkenyl, R<sup>32</sup>-substituted-(C<sub>1</sub>-C<sub>6</sub>)alkyl, R<sup>32</sup>-substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl and R<sup>32</sup>-substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>31</sup> is selected from the group consisting of H and (C<sub>1</sub>-C<sub>4</sub>)alkyl;

T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R<sup>32</sup> is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH, phenoxy, -CF<sub>3</sub>, -NO<sub>2</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, methylenedioxy, oxo, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfanyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, -N(CH<sub>3</sub>)<sub>2</sub>, -C(O)-NH(C<sub>1</sub>-C<sub>4</sub>)alkyl,

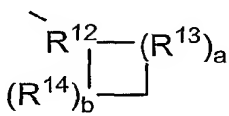
- 65 -

-C(O)-N((C<sub>1</sub>-C<sub>4</sub>)alkyl)<sub>2</sub>, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkoxy and pyrrolidinylcarbonyl; or R<sup>32</sup> is a covalent bond and R<sup>31</sup>, the nitrogen to which it is attached and R<sup>32</sup> form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indoliny or morpholiny group, or a (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indoliny or morpholiny group;

Ar<sup>1</sup> is aryl or R<sup>10</sup>-substituted aryl;

Ar<sup>2</sup> is aryl or R<sup>11</sup>-substituted aryl;

Q is a bond or, with the 3-position ring carbon of the azetidinone,

forms the spiro group ; and

R<sup>1</sup> is selected from the group consisting of

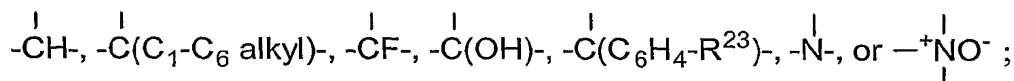
-(CH<sub>2</sub>)<sub>q</sub>-, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

-(CH<sub>2</sub>)<sub>e</sub>-E-(CH<sub>2</sub>)<sub>r</sub>-, wherein E is -O-, -C(O)-, phenylene, -NR<sup>22</sup>- or -S(O)<sub>0-2</sub>-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-(C<sub>2</sub>-C<sub>6</sub>)alkenylene-; and

-(CH<sub>2</sub>)<sub>f</sub>-V-(CH<sub>2</sub>)<sub>g</sub>-, wherein V is C<sub>3</sub>-C<sub>6</sub> cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R<sup>12</sup> is

-CH-, -C(C<sub>1</sub>-C<sub>6</sub> alkyl)-, -CF-, -C(OH)-, -C(C<sub>6</sub>H<sub>4</sub>-R<sup>23</sup>)-, -N-, or -<sup>+</sup>N<sup>+</sup>O<sup>-</sup>;

R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of -CH<sub>2</sub>-, -CH(C<sub>1</sub>-C<sub>6</sub> alkyl)-, -C(di-(C<sub>1</sub>-C<sub>6</sub> alkyl))-, -CH=CH- and -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-; or R<sup>12</sup> together with an adjacent R<sup>13</sup>, or R<sup>12</sup> together with an adjacent R<sup>14</sup>, form a -CH=CH- or a -CH=C(C<sub>1</sub>-C<sub>6</sub> alkyl)- group;

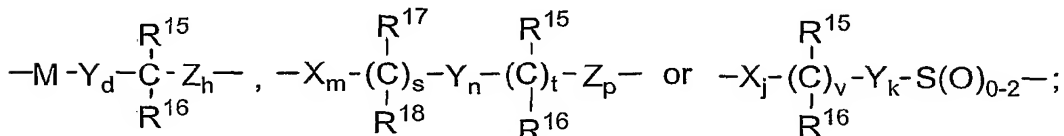
a and b are independently 0, 1, 2 or 3, provided both are not zero;

provided that when R<sup>13</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, a is 1;

provided that when R<sup>14</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, b is 1;

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provided that when a is 2 or 3, the R<sup>13</sup>'s can be the same or different; and  
 provided that when b is 2 or 3, the R<sup>14</sup>'s can be the same or different;  
 and when Q is a bond, R<sup>1</sup> also can be:



M is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-;

X, Y and Z are independently selected from the group consisting of -CH<sub>2</sub>-,  
 -CH(C<sub>1</sub>-C<sub>6</sub>)alkyl- and -C(di-(C<sub>1</sub>-C<sub>6</sub>)alkyl);

R<sup>10</sup> and R<sup>11</sup> are independently selected from the group consisting of 1-3  
 substituents independently selected from the group consisting of  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl, -OR<sup>19</sup>, -O(CO)R<sup>19</sup>, -O(CO)OR<sup>21</sup>, -O(CH<sub>2</sub>)<sub>1-5</sub>OR<sup>19</sup>,  
 -O(CO)NR<sup>19</sup>R<sup>20</sup>, -NR<sup>19</sup>R<sup>20</sup>, -NR<sup>19</sup>(CO)R<sup>20</sup>, -NR<sup>19</sup>(CO)OR<sup>21</sup>,  
 -NR<sup>19</sup>(CO)NR<sup>20</sup>R<sup>25</sup>, -NR<sup>19</sup>SO<sub>2</sub>R<sup>21</sup>, -COOR<sup>19</sup>, -CONR<sup>19</sup>R<sup>20</sup>, -COR<sup>19</sup>,  
 -SO<sub>2</sub>NR<sup>19</sup>R<sup>20</sup>, S(O)<sub>0-2</sub>R<sup>21</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>-COOR<sup>19</sup>, -O(CH<sub>2</sub>)<sub>1-10</sub>CONR<sup>19</sup>R<sup>20</sup>,  
 -(C<sub>1</sub>-C<sub>6</sub> alkylene)-COOR<sup>19</sup>, -CH=CH-COOR<sup>19</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub> and halogen;

R<sup>15</sup> and R<sup>17</sup> are independently selected from the group consisting of -OR<sup>19</sup>,  
 -O(CO)R<sup>19</sup>, -O(CO)OR<sup>21</sup> and -O(CO)NR<sup>19</sup>R<sup>20</sup>;

R<sup>16</sup> and R<sup>18</sup> are independently selected from the group consisting of H,  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl and aryl; or R<sup>15</sup> and R<sup>16</sup> together are =O, or R<sup>17</sup> and R<sup>18</sup> together  
 are =O;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4;

provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and

provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

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and when Q is a bond and R<sup>1</sup> is 
$$-X_j-\overset{\overset{R^{15}}{|}}{\underset{\underset{R^{16}}{|}}{(C)_v}}-Y_k-S(O)_{0-2}-$$
, Ar<sup>1</sup> can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R<sup>19</sup> and R<sup>20</sup> are independently selected from the group consisting of H,  
5 (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and aryl-substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>21</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl or R<sup>24</sup>-substituted aryl;

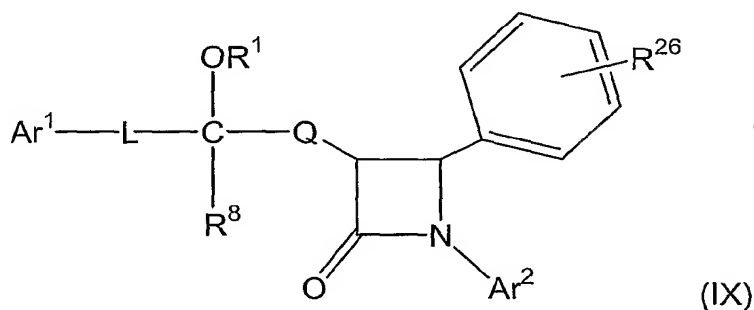
R<sup>22</sup> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)R<sup>19</sup> or -COOR<sup>19</sup>;

R<sup>23</sup> and R<sup>24</sup> are independently 1-3 groups independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, -COOH, NO<sub>2</sub>,

10 -NR<sup>19</sup>R<sup>20</sup>, -OH and halogeno; and

R<sup>25</sup> is H, -OH or (C<sub>1</sub>-C<sub>6</sub>)alkoxy; and

(g) Formula (IX):

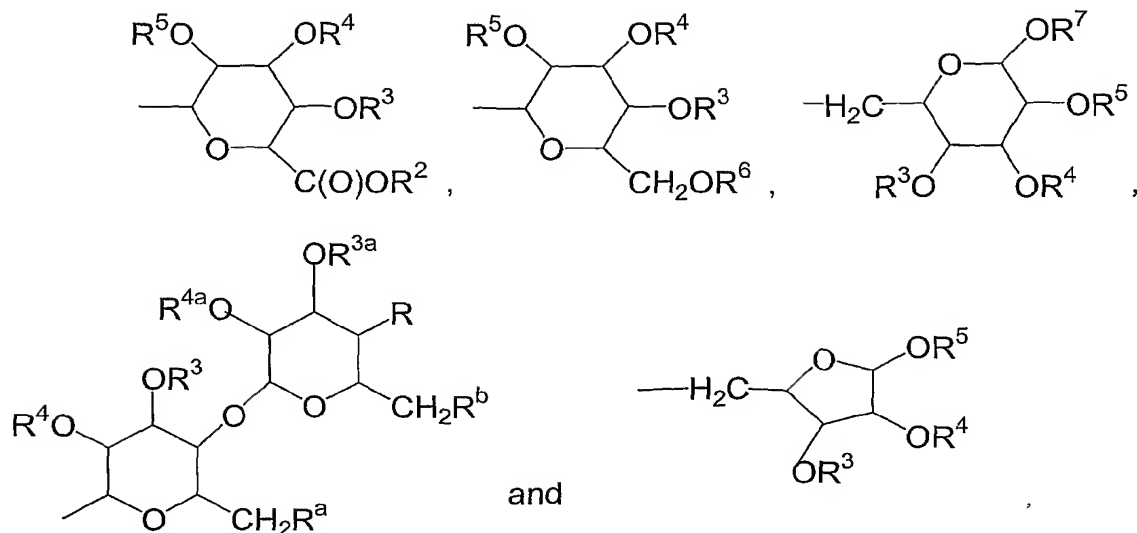


15 or a pharmaceutically acceptable salt or solvate thereof, wherein in Formula (IX):

R<sup>1</sup> is selected from the group consisting of H, G, G<sup>1</sup>, G<sup>2</sup>, -SO<sub>3</sub>H and -PO<sub>3</sub>H;

20 G is selected from the group consisting of: H,

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wherein  $R$ ,  $R^a$  and  $R^b$  are each independently selected from the group consisting of H, -OH, halo, -NH<sub>2</sub>, azido, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkoxy or -W- $R^{30}$ ;

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N( $R^{31}$ )-, -NH-C(O)-N( $R^{31}$ )- and -O-C(S)-N( $R^{31}$ )-;

$R^2$  and  $R^6$  are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, acetyl, aryl and aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

$R^3$ ,  $R^4$ ,  $R^5$ ,  $R^7$ ,  $R^{3a}$  and  $R^{4a}$  are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, acetyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl and -C(O)aryl;

$R^{30}$  is independently selected from the group consisting of  $R^{32}$ -substituted T,  $R^{32}$ -substituted-T-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  $R^{32}$ -substituted-(C<sub>2</sub>-C<sub>4</sub>)alkenyl,  $R^{32}$ -substituted-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  $R^{32}$ -substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl and  $R^{32}$ -substituted-(C<sub>3</sub>-C<sub>7</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

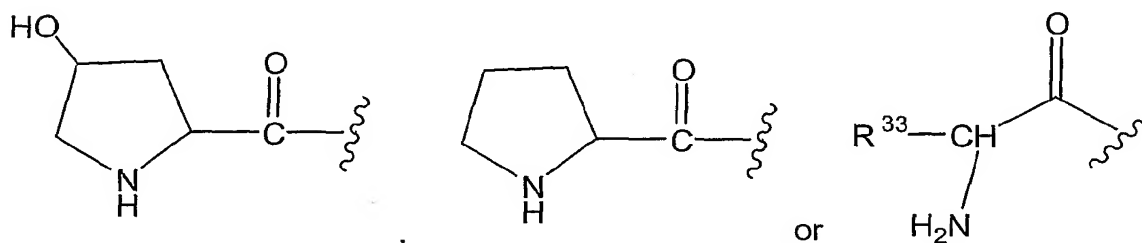
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$R^{31}$  is independently selected from the group consisting of H and (C<sub>1</sub>-C<sub>4</sub>)alkyl;

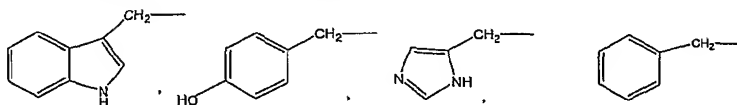
5 T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

10  $R^{32}$  is independently selected from 1-3 substituents which are each independently selected from the group consisting of H, halo, (C<sub>1</sub>-C<sub>4</sub>)alkyl, -OH, phenoxy, -CF<sub>3</sub>, -NO<sub>2</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, methylenedioxy, oxo, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfanyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, -N(CH<sub>3</sub>)<sub>2</sub>, -C(O)-NH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -C(O)-N((C<sub>1</sub>-C<sub>4</sub>)alkyl)<sub>2</sub>, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkyl, -C(O)-(C<sub>1</sub>-C<sub>4</sub>)alkoxy and pyrrolidinylcarbonyl; or  $R^{32}$  is a covalent bond and  $R^{31}$ , the nitrogen to which it is attached and  $R^{32}$  form  
15 a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholyl group, or a (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholyl group;

$G^1$  is represented by the structure:



20 wherein  $R^{33}$  is independently selected from the group consisting of unsubstituted alkyl,  $R^{34}$ -substituted alkyl, ( $R^{35}$ )( $R^{36}$ )alkyl-,



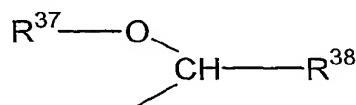
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$R^{34}$  is one to three substituents, each  $R^{34}$  being independently selected from the group consisting of  $\text{HOOC-}$ ,  $\text{HO-}$ ,  $\text{HS-}$ ,  $(\text{CH}_3)\text{S-}$ ,  $\text{H}_2\text{N-}$ ,  $(\text{NH}_2)(\text{NH})\text{C}(\text{NH})\text{-}$ ,  $(\text{NH}_2)\text{C}(\text{O})\text{-}$  and  $\text{HOOCCH}(\text{NH}_2^+)\text{CH}_2\text{SS-}$ ;

$R^{35}$  is independently selected from the group consisting of H and  $\text{NH}_2\text{-}$ ;

$R^{36}$  is independently selected from the group consisting of H, unsubstituted alkyl,  $R^{34}$ -substituted alkyl, unsubstituted cycloalkyl and  $R^{34}$ -substituted cycloalkyl;

$G^2$  is represented by the structure:



wherein  $R^{37}$  and  $R^{38}$  are each independently selected from the group consisting of  $(\text{C}_1\text{-C}_6)\text{alkyl}$  and aryl;

$R^{26}$  is one to five substituents, each  $R^{26}$  being independently selected from the group consisting of:

- a) H;
- b)  $\text{-OH}$ ;
- c)  $\text{-OCH}_3$ ;
- d) fluorine;
- e) chlorine;
- f)  $\text{-O-G}$ ;
- g)  $\text{-O-G}^1$ ;
- h)  $\text{-O-G}^2$ ;
- i)  $\text{-SO}_3\text{H}$ ; and
- j)  $\text{-PO}_3\text{H}$ ;

provided that when  $R^1$  is H,  $R^{26}$  is not H,  $\text{-OH}$ ,  $\text{-OCH}_3$  or  $\text{-O-G}$ ;

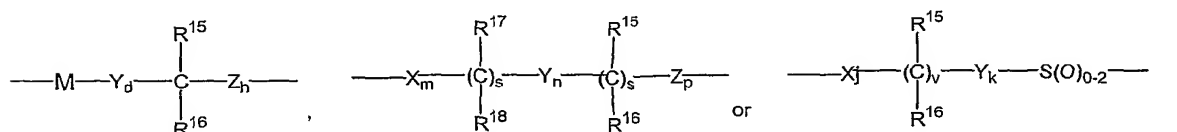
$\text{Ar}^1$  is aryl,  $R^{10}$ -substituted aryl, heteroaryl or  $R^{10}$ -substituted heteroaryl;

$\text{Ar}^2$  is aryl,  $R^{11}$ -substituted aryl, heteroaryl or  $R^{11}$ -substituted heteroaryl;

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L is selected from the group consisting of:

- a) a covalent bond;
- b)  $-(CH_2)_q-$ , wherein q is 1-6;
- 5 c)  $-(CH_2)_e-E-(CH_2)_r-$ , wherein E is  $-O-$ ,  $-C(O)-$ , phenylene,  $-NR^{22}-$  or  $-S(O)_{0-2}-$ , e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;
- d)  $-(C_2-C_6)alkenylene-$ ;
- e)  $-(CH_2)_f-V-(CH_2)_g-$ , wherein V is  $C_3-C_6$ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; and
- 10 f)



wherein M is  $-O-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

X, Y and Z are each independently selected from the group consisting of  
 15  $-CH_2-$ ,  $-CH(C_1-C_6)alkyl-$  and  $-C(di-(C_1-C_6)alkyl)-$ ;

$R^8$  is selected from the group consisting of H and alkyl;

$R^{10}$  and  $R^{11}$  are each independently selected from the group consisting of 1-  
 20 3 substituents which are each independently selected from the group consisting of  
 $(C_1-C_6)alkyl$ ,  $-OR^{19}$ ,  $-O(CO)R^{19}$ ,  $-O(CO)OR^{21}$ ,  $-O(CH_2)_{1-5}OR^{19}$ ,  $-$   
 $O(CO)NR^{19}R^{20}$ ,  $-NR^{19}R^{20}$ ,  $-NR^{19}(CO)R^{20}$ ,  $-NR^{19}(CO)OR^{21}$ ,  
 $-NR^{19}(CO)NR^{20}R^{25}$ ,  $-NR^{19}SO_2R^{21}$ ,  $-COOR^{19}$ ,  $-CONR^{19}R^{20}$ ,  $-COR^{19}$ ,  $-$   
 $SO_2NR^{19}R^{20}$ ,  $S(O)_{0-2}R^{21}$ ,  $-O(CH_2)_{1-10}COOR^{19}$ ,  $-O(CH_2)_{1-10}CONR^{19}R^{20}$ ,  $-$   
 25  $(C_1-C_6 alkylene)-COOR^{19}$ ,  $-CH=CH-COOR^{19}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$  and halo;

$R^{15}$  and  $R^{17}$  are each independently selected from the group consisting of  
 $-OR^{19}$ ,  $-OC(O)R^{19}$ ,  $-OC(O)OR^{21}$ ,  $-OC(O)NR^{19}R^{20}$ ;



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$R^{16}$  and  $R^{18}$  are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>6</sub>)alkyl and aryl;

5 or  $R^{15}$  and  $R^{16}$  together are =O, or  $R^{17}$  and  $R^{18}$  together are =O;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

s is 0 or 1;

10 t is 0 or 1;

m, n and p are each independently selected from 0-4;

provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, n and p is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

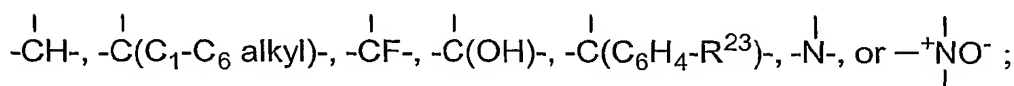
15 v is 0 or 1;

j and k are each independently 1-5, provided that the sum of j, k and v is 1-5;

Q is a bond,  $-(CH_2)_q-$ , wherein q is 1-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group



wherein  $R^{12}$  is

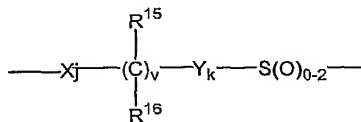


25  $R^{13}$  and  $R^{14}$  are each independently selected from the group consisting of  $-\text{CH}_2-$ ,  $-\text{CH}(\text{C}_1\text{-C}_6 \text{ alkyl})-$ ,  $-\text{C}(\text{di}-(\text{C}_1\text{-C}_6) \text{ alkyl})-$ ,  $-\text{CH}=\text{CH}-$  and  $-\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})=\text{CH}-$ ; or  $R^{12}$  together with an adjacent  $R^{13}$ , or  $R^{12}$  together with an adjacent  $R^{14}$ , form a  $-\text{CH}=\text{CH}-$  or a  $-\text{CH}=\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})-$  group;

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a and b are each independently 0, 1, 2 or 3, provided both are not zero;  
 provided that when R<sup>13</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, a is 1; provided that  
 when R<sup>14</sup> is -CH=CH- or -C(C<sub>1</sub>-C<sub>6</sub> alkyl)=CH-, b is 1; provided that when a is 2 or  
 3, the R<sup>13</sup>'s can be the same or different; and provided that when b is 2 or 3, the  
 R<sup>14</sup>'s can be the same or different;

and when Q is a bond and L is



then Ar<sup>1</sup> can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl,  
 thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R<sup>19</sup> and R<sup>20</sup> are each independently selected from the group consisting of H,  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl and aryl-substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>21</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl or R<sup>24</sup>-substituted aryl;

R<sup>22</sup> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl (C<sub>1</sub>-C<sub>6</sub>)alkyl, -C(O)R<sup>19</sup> or -COOR<sup>19</sup>;

R<sup>23</sup> and R<sup>24</sup> are each independently selected from the group consisting of 1-  
 3 substituents which are each independently selected from the group consisting of H,  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, -COOH, NO<sub>2</sub>, -NR<sup>19</sup>R<sup>20</sup>, -OH and halo; and

R<sup>25</sup> is H, -OH or (C<sub>1</sub>-C<sub>6</sub>)alkoxy.

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5. The method according to claim 1, wherein the at least one sterol absorption inhibitor is administered to a subject in an amount ranging from about 0.1 to about 1000 milligrams of sterol absorption inhibitor per day.

5 6. The method according to claim 1, further comprising the step of administering at least one other agent useful for the treatment of an autoimmune disorder to the subject.

10 7. The method according to claim 6, wherein the other agent useful for the treatment of an autoimmune disorder is selected from the group consisting of:

- a) disease modifying antirheumatic drugs;
- b) nonsteroidal anitnflammatory drugs;
- c) COX-2 selective inhibitors;
- d) COX-1 inhibitors;
- 15 e) immunosuppressives; p70<sup>S6</sup> kinase inhibitors; and inosine monophosphate dehydrogenase inhibitors;
- f) steroids;
- g) biological response modifiers; and
- h) other agents useful for the treatment of autoimmune disorders.

20 8. The method according to claim 1, further comprising the step of administering at least one HMG CoA reductase inhibitor to the subject.

25 9. The method according to claim 8, wherein the at least one HMG CoA reductase inhibitor is atorvastatin.

10. The method according to claim 8, wherein the at least one HMG CoA reductase inhibitor is simvastatin.

30 11. The method according to claim 1, wherein the subject has an autoimmune disorder selected from the group consisting of: Alopecia Areata, Ankylosing Spondylitis, Antiphospholipid Syndrome, Autoimmune Addison's Disease,

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Autoimmune Diabetes, Autoimmune Hemolytic Anemia, Autoimmune Hepatitis, Behcet's Disease, Bullous Pemphigoid, Cardiomyopathy, Celiac Sprue-Dermatitis, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Inflammatory Demyelinating Polyneuropathy, Churg-Strauss Syndrome, Cicatricial Pemphigoid, CREST Syndrome, Cold Agglutinin Disease, Crohn's Disease, Discoid Lupus, Essential Mixed Cryoglobulinemia, Fibromyalgia-Fibromyositis, Good Pasture Syndrome, Graft Versus Host Disease, Graves' Disease, Guillain-Barré, Hashimoto's Thyroiditis, Idiopathic Pulmonary Fibrosis, Idiopathic Thrombocytopenia Purpura (ITP), IgA Nephropathy, Insulin Dependent Diabetes, Juvenile Arthritis, Lichen Planus, Lupus, Ménière's Disease, Mixed Connective Tissue Disease, Multiple Sclerosis, Myasthenia Gravis, Myositis, Pemphigus Vulgaris, Pernicious Anemia, Polyarteritis Nodosa, Polychondritis, Polyglandular Syndromes, Polymyalgia Rheumatica, Polymyositis and Dermatomyositis, Primary Agammaglobulinemia, Primary Biliary Cirrhosis, Psoriasis, Raynaud's Phenomenon, Reiter's Syndrome, Rheumatic Fever, Rheumatoid Arthritis, Sarcoidosis, Scleroderma, Sjögren's Syndrome, Stiff-Man Syndrome, Takayasu Arteritis, Temporal Arteritis/Giant Cell Arteritis, Ulcerative Colitis, Uveitis, Vasculitis, Vitiligo, and Wegener's Granulomatosis.

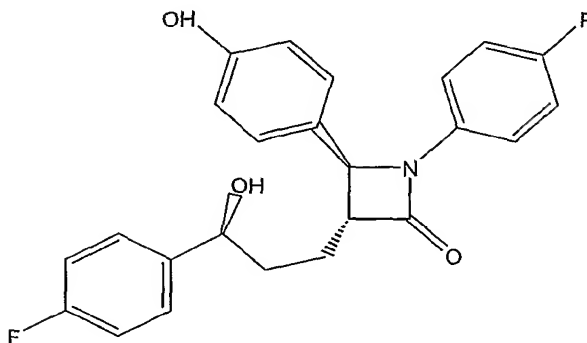
12. The method according to claim 1, wherein said sterol absorption inhibitor disrupts lipid raft formation and/or organization within the cell membranes of leukocytes.

13. The method according to claim 12, wherein said lipid raft disruption affects the pathogenesis of said autoimmune disorder by affecting at least one immune response selected from the group consisting of antigen presentation, T-cell activation, T-cell receptor signaling, adhesion molecule function, chemokine receptor signaling, and combinations thereof.

14. A method of treating or preventing an autoimmune disorder in a subject is provided, comprising the step of administering to a subject in need of such

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treatment an effective amount of at least one sterol absorption inhibitor represented by Formula (II) below:



(II)

5 or a pharmaceutically acceptable salt or solvate thereof.

15 The method according to claim 14, wherein the subject has an autoimmune disorder selected from the group consisting of: Alopecia Areata, Ankylosing Spondylitis, Antiphospholipid Syndrome, aplastic anemia, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinemia, pure red cell  
 10 aplasia, chronic neutropenias, amegakaryocytic thrombocytopenia, antiphospholipid syndromes, autoimmune thrombocytopenia, autoimmune hemolytic syndromes, antiphospholipid syndromes, autoimmune gastritis, achlorhydria, Autoimmune Addison's Disease, Autoimmune Diabetes, Autoimmune Hemolytic Anemia, Autoimmune Hepatitis, Autoimmune hypophysitis, Autoimmune orchiditis,  
 15 autoimmune ovarian failure, Behcet's Disease, Bullous Pemphigoid, Cardiomyopathy, Celiac Sprue-Dermatitis, Cicatricial pemphigoid, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Inflammatory Demyelinating Polyneuropathy, Interstitial cystitis, Churg-Strauss Syndrome, Cicatricial Pemphigoid, CREST Syndrome, Cold Agglutinin Disease, Crohn's Disease, Dermatitis herpetiformis, Discoid Lupus, Drug-induced autoimmune disorders, Endometriosis, Epidermolysis bullosa acquisita, Essential Mixed Cryoglobulinemia, Fibromyalgia-Fibromyositis, Glomerulonephritis, Good Pasture Syndrome, Graft Versus Host Disease, Graves' Disease, Guillain-Barré, Hashimoto's Thyroiditis,  
 20 Idiopathic Inflammatory Myopathies, Idiopathic Pulmonary Fibrosis, Idiopathic Thrombocytopenia Purpura (ITP), IgA Nephropathy, Insulin Dependent Diabetes,

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Juvenile Arthritis, Lichen Planus, Systemic Lupus Erythmatosus , Ménière's Disease, Metal-induced autoimmunity disorders, Mixed Connective Tissue Disease, Multiple Sclerosis, Myasthenia Gravis, Myocarditis, Myositis, Optic neuritis, Painless/postpartum thyroiditis, Peripheral nerve vasculitis, Pemphigus Foliaceus, Pemphigus Vulgaris, Pernicious Anemia, Polyarteritis Nodosa, Polychondritis, Polyglandular Syndromes, Polymyalgia Rheumatica, Polymyositis and Dermatomyositis, Postinfectious autoimmune disorders, Primary Agammaglobulinemia, Primary Biliary Cirrhosis, Psoriasis, Psoriatic Arthritis, Reactive Arthritis, Raynaud's Phenomenon, Reiter's Syndrome, Rheumatic Fever, Rheumatoid Arthritis, Sarcoidosis, Scleritis, Scleroderma, Sjögren's Syndrome, Stiff-Man Syndrome, Takayasu Arteritis, Temporal Arteritis/Giant-cell Arteritis, Ulcerative Colitis, Uveitis, Vasculitis, Vitiligo, and Wegener's Granulomatosis.

16. The method according to claim 14, further comprising the step of administering to said subject at least one other agent useful for the treatment of an autoimmune disorder.

17. The method according to claim 16, wherein the subject has rheumatoid arthritis and wherein said other agent is selected from the group consisting of COX-2 inhibitors, COX inhibitors, immunosuppressives, steroids, PDE IV inhibitors, anti-TNF- $\alpha$  compounds, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors and combinations thereof.

18. A method of treating or preventing rheumatoid arthritis in a subject, comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof.

19. A composition comprising: (a) at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof and (b) at least one other agent useful for the treatment of an autoimmune disorder.

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20. A therapeutic combination comprising: (a) a first amount of at least one sterol absorption inhibitor or a pharmaceutically acceptable salt or solvate thereof; and (b) a second amount of at least one other agent useful for the treatment of an autoimmune disorder, wherein the first amount and the second amount together  
5 comprise a therapeutically effective amount for the treatment or prevention of an autoimmune disorder in a subject.

21. Use of at least one compound of any of claims 1, 2, 3 or 4 for  
10 manufacture of a medicament for the treatment of an autoimmune disorder in a subject.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/35058

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K31/397 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, SCISEARCH, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03/082192 A (SMITHKLINE BEECHAM CORP ; MA CHUM (US); BHAT AJITA (US); FRAZEE JAM) 9 October 2003 (2003-10-09) page 23, line 10-30 -----	1, 11, 21
X	WO 02/070523 A (DIDIUK MARY THERESA ; GARIGIPATI RAVI SHANKER (US); LAU WAN FANG (U) 12 September 2002 (2002-09-12) page 13, line 29 -page 14, line 18; claims 8, 14 -----	1, 6, 7, 11, 18-21
X	WO 02/058734 A (SCHERING CORP) 1 August 2002 (2002-08-01) claims 19, 45 -----	19, 20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 April 2004

Date of mailing of the international search report

23/04/2004

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Authorized officer

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# INTERNATIONAL SEARCH REPORT

national application No.  
PCT/US 03/35058

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: —  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 1-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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## Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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## Continuation of Box I.2

Present claims 1-10, 12-14, 16 and 21 relate to a method/composition defined by reference to a desirable characteristics or properties, namely "sterol absorption inhibitor" and "autoimmune disorder".

The claims cover all methods/compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods/compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method/composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds I-XII mentioned in claims 2-4 and the diseases mentioned in claim 11.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/35058

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